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Contents

Editorial

Dear colleagues,

One major prerequisite for **personalized medicine** strategies in gastroenterology is the development and validation of **biomarkers** for disease prognosis and response to treatment. In the case of **Crohn's disease**, the first prospective study (PROFILE) of a promising biomarker for gene expression in cytotoxic T cells in peripheral blood showed that the biomarker has no value in routine clinical practice. Yet, the study was able to impressively prove that, after an initial diagnosis of Crohn's disease, early combination therapy consisting of infliximab and a thiopurine (**top down**) is clearly superior to conventional escalation (**step up**) (Noor et al., page 14). It may, however, be possible to infer indications of responses to treatment using **biomarkers from fecal tests**. Using the characterization of dysbiosis, stool moisture and calprotectin, it was possible to predict response to treatment with biologics with an accuracy of 73.9% in a prospective cohort of patients with inflammatory bowel disease (Caenepeel et al., page 19). But biomarkers are also urgently needed for early forecasting of the course of **acute pancreatitis**. Here, too, the gut flora appears to play a role – in a multicenter study, the composition of the oral-intestinal **microbiota** was thus better able to predict **the severity of acute pancreatitis** than conventional risk scores. Short-chain fatty acids, in particular, may be relevant for future diagnostic and treatment strategies (Ammer-Herrmenau et al., page 27).

Endoscopic ultrasonography-guided **gastroenterostomy** (GE) using **lumen-apposing metal stents (LAMS)** serves as a good alternative to the placement of **duodenal stents** in the case of malignant gastroparesis. Within the scope of a multicenter randomized study, it was possible to show that GE using LAMS performs significantly better in terms of stent patency, food intake, and the number of subsequent interventions, and should therefore be given preference for use in correspondingly specialized centers (Teoh et al., page 12). The pharmacological treatment options for **irritable bowel syndrome (IBS)** continue to be limited, and many patients associate the symptoms with "histamine intolerance". In light of these concerns, it is interesting that, in a randomized study with patients with non-constipated IBS, treatment with the **antihistamine ebastine** was significantly more effective than placebo (Decraecker et al., page 20).

Climate change and CO_2 emissions have a major effect on our day-to-day lives. Against this backdrop, the question arises as to what **ecological fingerprint** is left behind as a result of work in **interventional endoscopy**. This question was examined in two papers (Desai et al., page 11 and Henniger et al., page 12). It comes as no surprise that rational use of equipment and resources as well as packaging waste can lead to a considerably improved **environmental balance sheet** and should be given greater attention in the future.

In the case of **primary biliary cholangitis (PBC)**, a drop in alkaline phosphatase (ALP) levels to less than 1.5 times the upper limit of normal is usually deemed an adequate response to treatment. However, a current large-scale international cohort study shows that especially patients with advanced fibrosis and/or patients of a relatively young age benefit considerably from complete ALP normalization. Consequently, for these patients, supplementary therapy should be taken into consideration (Corpechot et al., page 32). In the case of **autoimmune hepatitis** as well, current findings indicate the relevance of a complete response to treatment: data from the retrospective registry of the International Autoimmune Hepatitis Group (IAIHG-RR) shows that a lack of complete biochemical response constitutes a major adverse prognosis factor (Slooter et al., page 33). For the first time, a specific drug has been approved in the United States for non-alcoholic steatohepatitis (NASH) or, according to the new nomenclature, **metabolic dysfunction-associated steatohepatitis (MASH)**. Resmetirom is an oral, liver-directed, thyroid hormone receptor β-selective agonist. In a randomized, controlled phase 3 study, resmetirom was superior to placebo in terms of MASH resolution as well as in terms of improvement of liver fibrosis (Harrison et al., page 30).

We very much hope that this small selection of papers has kindled your interest in reading these and other publications summarized in this issue in greater depth, and wish you enjoyable reading as well as happy and peaceful summer days!

Best wishes

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ESOPHAGUS TO SMALL INTESTINE

Celiac Disease, Gluten Sensitivity and Food Allergy

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de Graaf MCG, Lawton CL, Croden F, Smolinska A, Winkens B, Hesselink MAM, van Rooy G, Weegels PL, Shewry PR, Mooney PD, Houghton LA, Witteman BJM, Keszthelyi D, Brouns FJPH, Dye L, Jonkers DMAE

The effect of expectancy versus actual gluten intake on gastrointestinal and extra-intestinal symptoms in non-celiac gluten sensitivity: A randomized, double-blind, placebo-controlled, international, multi-center study

Background: Many individuals without celiac disease or wheat allergy reduce their gluten intake because they believe that gluten causes their gastrointestinal symptoms. Symptoms could be affected by negative expectancy. Therefore, the authors aimed to investigate the effects of expectancy versus actual gluten intake on symptoms in people with non-celiac gluten sensitivity (NCGS).
Methods: This randomized, double-blind, placebo-controlled, international, multicenter study was done at the University of Leeds (UK), Maastricht University (The Netherlands), and Wageningen University and Research (The Netherlands). People aged 18-70 years with self-reported NCGS (i.e., gastrointestinal symptoms within 8 hours of gluten consumption) without celiac disease and wheat allergy were recruited. Participants had to follow a gluten-free or gluten-restricted diet for at least 1 week before (and throughout) study participation and had to be asymptomatic or mildly symptomatic (overall gastrointestinal symptom score ≤ 30 mm on the Visual Analogue Scale [VAS]) while on the diet. Participants were randomly assigned (1:1:1:1; blocks of 8; stratified by site and gender) to 1 of 4 groups based on the expectation to consume gluten-containing (E^+) or gluten-free (E^-) oat bread for breakfast and lunch (2 slices each) and actual intake of gluten-containing (G^+) or gluten-free (G^-) oat bread. Participants, investigators, and those assessing outcomes were masked to the actual gluten assignment, and participants were also masked to the expectancy part of the study. The primary outcome was overall gastrointestinal symptom score on the VAS, which was measured at and corrected for baseline (before breakfast) and hourly for 8 hours, with lunch served after 4 hours, and analyzed per-protocol. Safety analysis included all participants incorporated in the per-protocol analysis.
Findings: Between October 19, 2018, and February 14, 2022, 165 people were screened and 84 were randomly assigned to E^+G^+ (n = 21), E^+G^- (n = 21), E^-G^+ (n = 20), or E^-G^- (n = 22). One person in the E^+G^+ group was excluded due to not following test day instructions, leaving 83 participants in the per-protocol analysis. Median age was 27.0 years (interquartile range, 21.0–45.0), 71 of 83 people (86%) were women, and 12 (14%) were men. Mean overall gastrointestinal symptom score was significantly higher for E^+G^+ (16.6 mm [95% confidence interval {CI}: 13.1–20.0]) than for E^-G^+ (6.9 mm [95% CI: 3.5–10.4]; difference 9.6 mm [95% CI: 3.0–16.2], p = 0.0010) and E^-G^- (7.4 mm [95% CI: 4.2–10.7]; difference 9.1 mm [95% CI: 2.7–15.6], p = 0.0016), but not for E^+G^- (11.7 mm [95% CI: 8.3–15.1]; difference 4.9 mm [95% CI: -1.7–11.5], p = 0.28). There was no difference between E^+G^- and E^-G^+ (difference 4.7 mm [95% CI: -1.8–11.3], p = 0.33), E^+G^- and E^-G^- (difference 4.2 mm [95% CI: -2.2–10.7], p = 0.47), and E^-G^+ and E^-G^- (difference -0.5 mm [95% CI: -7.0–5.9], p = 1.0). Adverse events were reported by 2 participants in the E^+G^- group (itching jaw [n = 1]; feeling lightheaded and stomach rumbling [n = 1]) and 1 participant in the E^-G^+ group (vomiting).

Interpretation: The combination of expectancy and actual gluten intake had the largest effect on gastrointestinal symptoms, reflecting a nocebo effect, although an additional effect of gluten cannot be ruled out. These results necessitate further research into the possible involvement of the gut-brain interaction in non-celiac gluten sensitivity.

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Aliment Pharmacol Ther. 2024;59(5):592–605

Maimaris S, Schiepatti A, Biagi F

Systematic review with meta-analysis: Cause-specific and all-cause mortality trends across different celiac disease phenotypes

Background: Data on mortality in celiac disease are contrasting.
Aims: To systematically review the literature on all-cause and cause-specific mortality in celiac disease compared to the general population, and evaluate differences across clinical phenotypes, geographical regions, and over time.
Methods: The authors searched PubMed and Embase from January 1, 1970, to December 31, 2022, for eligible studies reporting on all-cause and cause-specific mortality in celiac disease compared to the general population or controls.
Results: They included 25 studies. All-cause mortality (hazard ratio [HR] = 1.16, 95% confidence interval [CI]: 1.05–1.27, I^2 = 89%), mortality due to malignancies (HR = 1.21, 95% CI: 1.08–1.36, I^2 = 65%) and respiratory disease (HR = 1.39, 95% CI: 1.04–1.86, I^2 = 76%) were increased. Mortality due to non-Hodgkin lymphoma (HR = 10.14, 95% CI: 2.19–46.88, I^2 = 96%) was markedly increased. Mortality significantly decreased in recent decades: 1989–2004 (HR = 1.61, 95% CI: 1.27–2.03, I^2 = 91%),

2005–2014 (HR = 1.16, 95% CI: 0.99–1.36, I^2 = 89%), 2015–2022 (HR = 1.19, 95% CI: 1.05–1.35, I^2 = 93%). All-cause mortality was not increased in dermatitis herpetiformis (HR = 0.85, 95% CI: 0.73–0.99, I^2 = 40%) and undiagnosed celiac disease (HR = 1.09, 95% CI: 0.95–1.25, I^2 = 0%). Mortality was increased in the United Kingdom (HR = 1.23, 95% CI: 1.03–1.47, I^2 = 91%) but not Scandinavia (HR = 1.01, 95% CI: 0.91–1.13, I^2 = 81%). Limitations include high heterogeneity and lack of data for many countries.

Conclusion: Mortality in celiac disease is increased, predominantly due to malignancies – particularly non-Hodgkin lymphoma – although differing significantly across disease phenotypes. Mortality of patients with celiac disease has significantly decreased in recent decades. These results may influence diagnosis and management.

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Wood RA, Togias A, Sicherer SH, Shreffler WG, Kim EH, Jones SM, Leung DYM, Vickery BP, Bird JA, Spergel JM, Iqbal A, Olsson J, Ligueros-Saylan M, Uddin A, Calatroni A, Huckabee CM, Rogers NH, Yovetich N, Dantzer J, Mudd K, Wang J, Groetch M, Pyle D, Keet CA, Kulis M, Sindher SB, Long A, Scurlock AM, Lanser BJ, Lee T, Parrish C, Brown-Whitehorn T, Spergel AKR, Veri M, Hamrah SD, Brittain E, Poyser J, Wheatley LM, Chinthrajah RS

Omalizumab for the treatment of multiple food allergies

Background: Food allergies are common and are associated with substantial morbidity; the only approved treatment is oral immunotherapy for peanut allergy.
Methods: In this trial, the authors assessed whether omalizumab, a monoclonal anti-immunoglobulin E (IgE) antibody, would be effective and safe as monotherapy in patients with multiple food allergies. Persons 1–55 years of age who were allergic to peanuts and at least 2 other trial-specified foods (cashew, milk, egg, walnut, wheat, and hazelnut) were screened. Inclusion required a reaction to a food challenge of ≤ 100 mg of peanut protein and ≤ 300 mg of the 2 other foods. Participants were randomly assigned, in a 2:1 ratio, to receive omalizumab or placebo administered subcutaneously (with the dose based on weight and IgE levels) every 2–4 weeks for 16–20 weeks, after which the challenges were repeated. The primary end point was ingestion of peanut protein in a single dose of ≥ 600 mg without dose-limiting symptoms. The 3 key secondary end points were the consumption of cashew, of milk, and of egg in single doses of at least 1000 mg each without dose-limiting symptoms. The first 60 participants (59 of whom were children or adolescents) who completed this first stage were enrolled in a 24-week open-label extension.
Results: Of the 462 persons who were screened, 180 underwent randomization. The analysis population consisted of the 177 children and adolescents (1–17 years of age). A total of 79 of the 118 participants (67%) receiving omalizumab met the primary end-point criteria, as compared with 4 of the 59 participants (7%) receiving placebo ($p < 0.001$). Results for the key secondary end points were consistent with those of the primary end point (cashew, 41% vs. 3%; milk, 66% vs. 10%; egg, 68% vs. 0%; $p < 0.001$ for all comparisons). Safety end points did not differ between the groups, aside from more injection-site reactions in the omalizumab group.

Conclusions: In persons as young as 1 year of age with multiple food allergies, omalizumab treatment for 16 weeks was superior to placebo in increasing the reaction threshold for peanut and other common food allergens.

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Achalasia and Motility Disorders

J Clin Gastroenterol. 2024;58(3):247–52

Marshall A, Fai C, Han J, Yule AM, Jangi S

Rising inpatient utilization and costs of cannabis hyperemesis syndrome hospitalizations in Massachusetts after cannabis legalization

Goals: The authors described the demographics, inpatient utilization, and cost of services among patients hospitalized for putative cannabinoid hyperemesis syndrome (CHS) predating and postdating cannabis legalization in Massachusetts.
Background: As the recreational use of cannabis has been widely legalized nationally, the resulting shifts in clinical presentation, health care utilization, and estimated costs of CHS hospitalizations remain unclear in the postlegalization era.
Study: The authors performed a retrospective cohort study among patients admitted to a large urban hospital between 2012 and 2021, before and after the date of cannabis legalization in Massachusetts (December 15, 2016). They examined the demographic and clinical characteristics of patients admitted for putative CHS, the utilization of hospital services, and estimated inpatient costs pre- and postlegalization.
Results: A significant increase in putative CHS hospitalizations pre- and post-cannabis legalization in Massachusetts was identified (0.1% vs. 0.02% of total admissions per time period, $p < 0.05$). Across 72 CHS hospitalizations, patient demographics were similar pre- and postlegalization. Hospital resource utilization increased postlegalization, with increased length of stay (3 days vs. 1 day, $p < 0.005$), and need for antiemetics ($p < 0.05$). Multivariate linear regression confirmed that postlegalization admissions were independently associated with increased length of stay ($B = 5.35$, $p < 0.05$). The mean cost of hospitalization was significantly higher postlegalization ($18,714 vs. $7460, $p < 0.0005$), even after adjusting for medical inflation ($18,714 vs. $8520, $p < 0.001$)

with intravenous fluid administration and endoscopy costs increased ($p < 0.05$). On multivariate linear regression, hospitalization for putative CHS during postlegalization predicted increased costs (B = 10,131.25, $p < 0.05$).

Conclusions: In the postlegalization era of cannabis in Massachusetts, increased putative cannabinoid hyperemesis syndrome hospitalizations were found, with a concomitant increased length of hospital stay and total cost per hospitalization. As cannabis use increases, the recognition and costs of its deleterious effects are necessary to incorporate into future clinical practice strategies and health policy.

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Reflux

Gastroenterology. 2024;166(1):132–8.e3

Åkerström JH, Santoni G, von Euler Chelpin M, Ness-Jensen E, Kauppila JH, Holmberg D, Lagergren J

Antireflux surgery versus antireflux medication and risk of esophageal adenocarcinoma in patients with Barrett's esophagus

Background and aims: Antireflux treatment is recommended to reduce esophageal adenocarcinoma (EAC) in patients with Barrett's esophagus (BE). Antireflux surgery (fundoplication) counteracts gastroesophageal reflux of all types of carcinogenic gastric content and reduces esophageal acid exposure to a greater extent than antireflux medication (e.g., proton-pump inhibitors). The authors examined the hypothesis that antireflux surgery prevents EAC to a larger degree than antireflux medication in patients with BE.
Methods: This multinational and population-based cohort study included all patients with a diagnosis of BE in any of the national patient registries in Denmark (2012–2020), Finland (1987–1996 and 2010–2020), Norway (2008–2020), or Sweden (2006–2020). Patients who underwent antireflux surgery were compared with non-operated patients using antireflux medication. The risk of EAC was calculated using multivariable Cox regression, providing hazard ratios (HRs) and 95% confidence intervals (CIs) adjusted for age, sex, country, calendar year, and comorbidity.
Results: The cohort consisted of 33,939 patients with BE. Of these, 542 (1.6%) had undergone antireflux surgery. During up to 32 years of follow-up, the overall HR was not decreased in patients having undergone antireflux surgery compared with non-operated patients using antireflux medication, but rather increased (adjusted HR = 1.9; 95% CI: 1.1–3.5). In addition, HRs did not decrease with longer follow-up, but instead increased for each follow-up category, from 1.8 (95% CI: 0.6–5.0) within 1–4 years of follow-up to 4.4 (95% CI: 1.4–13.5) after 10–32 years of follow-up.

Conclusions: Patients with Barrett's esophagus who undergo antireflux surgery do not seem to have a lower risk of esophageal adenocarcinoma than those using antireflux medication.

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Gut. 2024;73(2):246–54

Liu BD, Udemba SC, Liang K, Tarabichi Y, Hill H, Fass R, Song G

Shorter-acting glucagon-like peptide-1 receptor agonists are associated with increased development of gastroesophageal reflux disease and its complications in patients with type 2 diabetes mellitus: A population-level retrospective matched cohort study

Background: Shorter half-life glucagon-like peptide-1 receptor agonists (GLP-1 RAs) delay gastric emptying (DGE) more than GLP-1 RAs with longer half-lives. DGE is a known risk factor for gastroesophageal reflux disease (GERD) and its complications.
Aim: To determine whether short-acting or long-acting GLP-1 RAs are associated with an increased risk of new GERD or GERD-related complications
Design: The authors used the TriNetX global database to identify adult patients with type 2 diabetes mellitus and generated 2 cohorts totaling 1,543,351 patients on (1) GLP-1 RA or (2) other second-line diabetes medication. Using propensity-score matching, Kaplan-Meier analysis and Cox-proportional hazards ratio (HR), they analyzed outcomes and separately examined outcomes in patients starting short-acting (≤ 1 day) and long-acting (≥ 5 days) GLP-1 RAs.
Results: 177,666 patients were in each propensity-matched cohort. GLP-1 RA exposure was associated with an increased risk (HR = 1.15; 95% confidence interval [CI]: 1.09–1.22) of erosive reflux disease (ERD). However, this was solely due to short-acting (HR = 1.215; 95% CI: 1.111–1.328), but not long-acting (HR = 0.994; 95% CI: 0.924–1.069) GLP-1 RA exposure. Short-acting GLP-1 RAs were also associated with increased risk of esophageal stricture (HR = 1.284; 95% CI: 1.135–1.453), Barrett's without dysplasia (HR = 1.372; 95% CI: 1.217–1.546) and Barrett's with dysplasia (HR = 1.505; 95% CI: 1.164–1.946) whereas long-acting GLP-1 RAs were not. This association persisted in sensitivity analyses, and when individually examining the short-acting GLP-1 RAs liraglutide, lixisenatide and exenatide.

Conclusion: Starting shorter-acting glucagon-like peptide-1 receptor agonists is associated with increased risks of gastroesophageal reflux disease and its complications.

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Gastritis and Helicobacter Pylori

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Pabón-Carrasco M, Keco-Huerga A, Castro-Fernández M, Saracino IM, Fiorini G, Vaira D, Pérez-Aísa Á, Tepes B, Jonaitis L, Voynovan I, Lucendo AJ, Lanas Á, Martínez-Domínguez SJ, Almajano EA, Rodrigo L, Vologzanina L, Brglez Jurecic N, Denkovski M, Bujanda L, Abdulkhakov RA, Huguet JM, Fernández-Salazar L, Alcaide N, Velayos B, Silkanovna Sarsenbaeva A, Zaytsev O, Ilchishina T, Barrio J, Bakulin I, Perona M, Alekseenko S, Romano M, Gravina AG, Núñez Ó, Gómez Rodríguez BJ, Ledro-Cano D, Pellicano R, Bogomolov P, Domínguez-Cajal M, Almela P, Gomez-Camarero J, Bordin DS, Gasbarrini A, Kupčinskas J, Cano-Català A, Moreira L, Nyssen OP, Mégraud F, O'Morain C, Gisbert JP; Hp-EuReg Investigators

Role of proton-pump inhibitors dosage and duration in Helicobacter pylori eradication treatment: Results from the European Registry on H. pylori management

Background: Management of Helicobacter pylori infection requires co-treatment with proton-pump inhibitors (PPIs) and the use of antibiotics to achieve successful eradication.
Aim: To evaluate the role of dosage of PPIs and the duration of therapy in the effectiveness of H. pylori eradication treatments based on the 'European Registry on Helicobacter pylori management' (Hp-EuReg).
Methods: Hp-EuReg is a multicenter, prospective, non-interventionist, international registry on the routine clinical practice of H. pylori management by European gastroenterologists. All infected adult patients were systematically registered from 2013 to 2022.
Results: Overall, 36,579 patients from 5 countries with more than 1000 patients were analyzed. Optimal (≥ 90%) first-line-modified intention-to-treat effectiveness was achieved with the following treatments: (1) 14-day therapies with clarithromycin-amoxicillin-bismuth and metronidazole-tetracycline-bismuth, both independently of the PPI dose prescribed; (2) All 10-day (except 10-day standard triple therapy) and 14-day therapies with high-dose PPIs; and (3) 10-day quadruple therapies with clarithromycin-amoxicillin-bismuth, metronidazole-tetracycline-bismuth, and clarithromycin-amoxicillin-metronidazole (sequential), all with standard-dose PPIs. In first-line treatment, optimal effectiveness was obtained with high-dose PPIs in all 14-day treatments, in 10- and 14-day bismuth quadruple therapies and in 10-day sequential with standard-dose PPIs. Optimal second-line effectiveness was achieved with (1) metronidazole-tetracycline-bismuth quadruple therapy for 14 and 10 days with standard and high-dose PPIs, respectively; and (2) levofloxacin-amoxicillin triple therapy for 14 days with high-dose PPIs. None of the 7-day therapies in both treatment lines achieved optimal effectiveness.

Conclusions: The authors recommend, in first-line treatment, the use of high-dose proton-pump inhibitors (PPIs) in 14-day triple therapy and in 10- or 14-day quadruple concomitant therapy in first-line treatment, while standard-dose PPIs would be sufficient in 10-day bismuth quadruple therapies. On the other hand, in second-line treatment, high-dose PPIs would be more beneficial in 14-day triple therapy with levofloxacin and amoxicillin or in 10-day bismuth quadruple therapy either as a 3-in-1 single capsule or in the traditional scheme.

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Helicobacter pylori treatment and gastric cancer risk after endoscopic resection of dysplasia: A nationwide cohort study

Background and aims: The study investigated the association between Helicobacter pylori treatment and the risk of gastric cancer (GC) after endoscopic resection of gastric dysplasia.
Methods: Patients who received endoscopic resection for gastric dysplasia between 2010 and 2020 from Korean nationwide insurance data were included. The authors verified the occurrence of new-onset GC and metachronous gastric neoplasm, which encompasses both cancer and dysplasia, > 1 year after the index endoscopic resection. Newly diagnosed GC ≥ 3 years and ≥ 5 years was regarded as late-onset GC. A multivariable Cox regression model with H. pylori treatment status as a time-dependent covariate was used to determine the risk of GC and metachronous gastric neoplasms.
Results: Gastric dysplasia in 69,722 patients was treated with endoscopy, and 49.5% were administered H. pylori therapy. During the median 5.6 years of follow-up, GC developed in 2406 patients and metachronous gastric neoplasms developed in 3342 patients. Receiving H. pylori therapy was closely related to lower GC risk (adjusted hazard ratio [aHR] = 0.88; 95% confidence interval [CI]: 0.80-0.96). H. pylori treatment also significantly decreased metachronous gastric neoplasm development (aHR = 0.76; 95% CI: 0.70-0.82). Furthermore, H. pylori therapy showed a prominent protective effect for late-onset GC development at ≥ 3 years (aHR = 0.84; 95% CI: 0.75–0.94) and ≥ 5 years (aHR = 0.80; 95% CI: 0.68–0.95).

Conclusions: In this nationwide cohort, Helicobacter pylori therapy after endoscopic resection of gastric dysplasia was associated with a reduced risk of gastric cancer and metachronous gastric neoplasm occurrence.

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EoE

United European Gastroenterol J. 2024;12(1):34–43

Uchida AM, Garber JJ, Pyne A, Peterson K, Roelstraete B, Olén O, Halfvarson J, Ludvigsson JF

Eosinophilic esophagitis is associated with increased risk of later inflammatory bowel disease in a nationwide Swedish population cohort

Background: Earlier studies on the possible association between eosinophilic esophagitis (EoE) and inflammatory bowel disease (IBD) have been contradictory.
Methods: Patients with biopsy-verified EoE diagnosed between 1990 and 2017 in Sweden (n = 1587) were age- and sex-matched with up to 5 general population reference individuals (n = 7808). EoE was defined using pathology reports from all 28 pathology centers in Sweden (the ESPRESSO study). Multivariate Cox regression then estimated hazard ratios (HRs) or future IBD. IBD was defined based on the international classification of disease codes and histopathology codes. In secondary analyses, sibling comparators were used to further reduce potential familial confounding. Additionally, the authors performed logistic regression examining earlier IBD in EoE.
Results: During follow-up until 2020, 16 (0.01%) EoE patients and 21 (0.003%) general population reference individuals diagnosed with IBD, corresponding to a 3.5-fold increased risk of future IBD (adjusted HR [aHR] = 3.56; 95% confidence interval [CI]: 1.79–7.11). EoE was linked to Crohn's disease (aHR = 3.39; 95% CI: 1.02–9.60) but not to ulcerative colitis (aHR = 1.37; 95% CI: 0.38–4.86). Compared to their siblings, patients with EoE were at a 2.48-fold increased risk of IBD (aHR = 2.48; 95% CI: 0.92–6.70). Earlier IBD was 15 times more likely in EoE patients than in matched reference individuals (odds ratio = 15.39; 95% CI: 7.68–33.59).

Conclusion: In this nationwide cohort study, eosinophilic esophagitis was associated with a 3.5-fold increased risk of later inflammatory bowel disease diagnosis. This risk increase may be due to shared genetic or early environmental risk factors, but also surveillance bias could play a role.

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Lee CJ, Dellon ES

Real-world efficacy of dupilumab in severe, treatment-refractory, and fibrostenotic patients with eosinophilic esophagitis

Background and aims: Dupilumab is approved for treatment of eosinophilic esophagitis (EoE), but real-world data are lacking. The authors aimed to determine the real-world efficacy of dupilumab in patients with severe, treatment-refractory, and fibrostenotic EoE.
Methods: They conducted a retrospective cohort study of EoE patients prescribed dupilumab and who were treatment-refractory to standard modalities. Patient demographics, clinical characteristics, EoE history, and procedural data (including the histologically worst, predupilumab, and postdupilumab endoscopies) were extracted from medical records. Symptomatic, endoscopic, and histologic responses were assessed for the worst and predupilumab endoscopies compared with the postdupilumab endoscopy.
Results: 46 patients with refractory fibrostenotic EoE who were treated with dupilumab were identified. Patients showed endoscopic, histologic, and symptomatic improvement on dupilumab compared with both the worst and the predupilumab esophagogastroduodenoscopies. The peak eosinophil counts decreased markedly, and postdupilumab histologic response rates were 80% and 57% for < 15 eosinophils per high-power field and ≤ 6 eosinophils per high-power field, respectively, and the Endoscopic Reference Score decreased from 5.01 to 1.89 ($p < 0.001$ for all). Although the proportion of strictures was stable, there was a significant increase in the predilation esophageal diameter (from 13.9 to 16.0 mm; $p < 0.001$). Global symptom improvement was reported in 91% ($p < 0.001$).

Conclusions: In this population of severe, refractory, and fibrostenotic patients with eosinophilic esophagitis (EoE), most achieved histologic, endoscopic, and symptom improvement with a median of 6 months of dupilumab, and esophageal stricture diameter improved. Dupilumab has real-world efficacy for a severe EoE population, most of whom would not have qualified for prior clinical trials.

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Bredenoord AJ, Dellon ES, Hirano I, Lucendo AJ, Schlag C, Sun X, Glotfelty L, Mannent L, Maloney J, Laws E, Mortensen E, Shabbir A

Dupilumab demonstrated efficacy and was well tolerated regardless of prior use of swallowed topical corticosteroids in adolescent and adult patients with eosinophilic esophagitis: A subgroup analysis of the phase 3 LIBERTY EoE TREET study

Objective: To assess the effect of long-term dupilumab on histological, symptomatic and endoscopic aspects of eosinophilic esophagitis (EoE) in adolescent and adult patients with and without prior use of swallowed topical corticosteroids (STC) or prior inadequate response, intolerance or contraindication to STC.
Design: Pre-specified analysis of data from the phase 3 LIBERTY EoE TREET study on patients who received dupilumab 300 mg once a week or placebo for 24 weeks (W24) in parts A and B, and an additional 28 weeks

(W52) in part C. Patients were categorized as with/without prior STC use and with/without inadequate/intolerance/contraindication to STC. The proportion of patients achieving ≤ 6 eosinophils per high-power field (eos/hpf), absolute change in Dysphagia Symptom Questionnaire (DSQ) score, mean change in Endoscopic Reference Score and Histologic Scoring System grade/stage scores were assessed for each subgroup.
Results: Regardless of prior STC use, dupilumab increased the proportion of patients achieving ≤ 6 eos/hpf and improved DSQ score versus placebo at W24, with improvements maintained or improved at W52. The DSQ score and the proportion of patients achieving ≤ 6 eos/hpf after switching from placebo to dupilumab at W24 were similar to those observed in the dupilumab group at W24, regardless of prior STC use or inadequate/intolerance/contraindication to STC. Improvements in other outcomes with dupilumab were similar in patients with/without prior STC use or inadequate/intolerance/contraindication to STC.

Conclusion: Dupilumab 300 mg once a week demonstrated efficacy and was well tolerated in patients with eosinophilic esophagitis regardless of prior swallowed topical corticosteroid (STC) use or inadequate response, intolerance and/or contraindication to STC.

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Barrett's Esophagus, Esophageal and Gastric Cancer

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Sun D, Mülder DT, Li Y, Nieboer D, Park JY, Suh M, Hamashima C, Han W, O'Mahony JF, Lansdorp-Vogelaar I

The effect of nationwide organized cancer screening programs on gastric cancer mortality: A synthetic control study

Background and aims: Nationwide organized gastric cancer (GC) screening programs have been running for decades in South Korea and Japan. This study conducted a quasi-experimental analysis to assess the population impact of these programs on GC mortality.
Methods: The authors used the flexible synthetic control method (SCM) to estimate the effect of the screening programs on age-standardized GC mortality and other upper gastrointestinal (UGI) diseases (esophageal cancer and peptic ulcer) among people aged ≥ 40 years. World Health Organization mortality data and country-level covariates from the World Bank and the Global Burden of Diseases study were used for the analyses. The authors compared postintervention trends in outcome with the counterfactual trend of the synthetic control and estimated average postintervention rate ratios (RRs) with associated 95% confidence intervals (CIs). A series of sensitivity analyses were conducted.
Results: The preintervention fits were acceptable for the analyses of South Korea's and Japan's GC mortality but poor for Japan's other UGI disease mortality. The average postintervention RRs were 0.83 (95% CI: 0.71–0.96) for GC mortality and 0.72 (95% CI: 0.57–0.90) for other UGI disease mortality in South Korea. The RR reached 0.59 by the 15th year after the initiation of nationwide screening. For Japan, the average RRs were 0.97 (95% CI: 0.88–1.07) for GC mortality and 0.93 (95% CI: 0.68–1.28) for other UGI disease mortality. Sensitivity analysis reveals the result for Japan may potentially be biased.

Conclusions: South Korea's nationwide gastric cancer screening has apparent benefits, whereas the Japanese program's effectiveness is uncertain. The experiences of South Korea and Japan could serve as a reference for other countries.

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Dhaliwal L, Kamboj AK, Williams JL, Chandar AK, Sachdeva K, Gibbons E, Lansing R, Passe M, Perez JA, Avenir KLR, Martin SA, Leggett CL, Chak A, Falk GW, Wani S, Shaheen NJ, Kisiel JB, Iyer PG

Prevalence and predictors of Barrett's esophagus after negative initial endoscopy: Analysis from 2 national databases

Background and aims: Guidelines suggest a single screening esophagogastroduodenoscopy (EGD) in patients with multiple risk factors for Barrett's esophagus (BE). The authors aimed to determine BE prevalence and predictors on repeat EGD after a negative initial EGD, using 2 large national databases (GI Quality Improvement Consortium [GIQuIC] and TriNetX).
Methods: Patients who underwent at least 2 EGDs were included and those with BE or esophageal adenocarcinoma detected at initial EGD were excluded. Patient demographics and prevalence of BE on repeat EGD were collected. Multivariate logistic regression was performed to assess for independent risk factors for BE detected on the repeat EGD.
Results: In 214,318 and 153,445 patients undergoing at least 2 EGDs over a median follow-up of 28–35 months, the prevalence of BE on repeat EGD was 1.7% in GIQuIC and 3.4% in TriNetX, respectively (26–45% of baseline BE prevalence). Most patients (89%) had non-dysplastic BE. The prevalence of BE remained stable over time (from 1 year to > 5 years from negative initial EGD) but increased with increasing number of risk factors. BE prevalence in a high-risk population (gastroesophageal reflux disease plus ≥ 1 risk factor for BE) was 3–4%.

Conclusions: In this study of > 350,000 patients, rates of Barrett's esophagus (BE) on repeat esophagogastroduodenoscopy ranged from 1.7–3.4%, and were higher in those with multiple risk factors. Most were likely missed at initial evaluation, underscoring the importance of a high-quality initial endoscopic examination. Although routine repeat endoscopic BE screening after a negative initial examination is not recommended, repeat screening may be considered in carefully selected

patients with gastroesophageal reflux disease and ≥ 2 risk factors for BE, potentially using non-endoscopic tools.

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Shitara K, Rha SY, Wyrwicz LS, Oshima T, Karaseva N, Osipov M, Yasui H, Yabusaki H, Afanasyev S, Park YK, Al-Batran SE, Yoshikawa T, Yanez P, Di Bartolomeo M, Lonardi S, Tabernero J, Van Cutsem E, Janjigian YY, Oh DY, Xu J, Fang X, Shih CS, Bhagia P, Bang YJ; KEYNOTE-585 investigators

Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastroesophageal cancer (KEYNOTE-585): An interim analysis of the multicenter, double-blind, randomized phase 3 study

Background: The benefit of combination neoadjuvant and adjuvant chemotherapy and immune checkpoint inhibition in patients with locally advanced, resectable gastric or gastroesophageal adenocarcinoma is unknown. The authors assess the antitumor activity of neoadjuvant and adjuvant pembrolizumab plus chemotherapy in patients with locally advanced resectable gastric or gastroesophageal adenocarcinoma.
Methods: The KEYNOTE-585 study is a multicenter, randomized, placebo-controlled, double-blind, phase 3 study done at 143 medical centers in 24 countries. Eligible patients were aged ≥ 18 years with untreated, locally advanced, resectable gastric or gastroesophageal adenocarcinoma, and an Eastern Cooperative Oncology Group performance status 0–1. Patients were randomly assigned (1:1) by an interactive voice response system and integrated web response system to neoadjuvant pembrolizumab 200 mg intravenously or placebo (saline) plus cisplatin-based doublet chemotherapy (main cohort) every 3 weeks for 3 cycles, followed by surgery, adjuvant pembrolizumab or placebo plus chemotherapy for 3 cycles, then adjuvant pembrolizumab or placebo for 11 cycles. A small cohort was also randomly assigned (1:1) to pembrolizumab or placebo plus fluorouracil, docetaxel, and oxaliplatin (FLOT)-based chemotherapy (FLOT cohort) every 2 weeks for 4 cycles, followed by surgery, adjuvant pembrolizumab, or placebo plus FLOT for 4 cycles, then adjuvant pembrolizumab or placebo for 11 cycles. Patients were stratified by geographic region, tumor stage, and chemotherapy backbone. Primary end points were pathological complete response (reviewed centrally), event-free survival (reviewed by the investigator), and overall survival in the intention-to-treat population, and safety assessed in all patients who received at least 1 dose of study treatment.
Findings: Between October 9, 2017, and January 25, 2021, of 1254 patients screened, 804 were randomly assigned to the main cohort, of whom 402 were assigned to the pembrolizumab plus cisplatin-based chemotherapy group and 402 to the placebo plus cisplatin-based chemotherapy group, and 203 to the FLOT cohort, of whom 100 were assigned to the pembrolizumab plus FLOT group and 103 to placebo plus FLOT group. In the main cohort of 804 participants, 575 (72%) were male and 229 (28%) were female. In the main cohort, after median follow-up of 47.7 months (interquartile range, 38.0–54.8), pembrolizumab was superior to placebo for pathological complete response (52/402 [12.9%; 95% confidence interval {CI}: 9.8–16.6] vs. 8/402 [2.0%; 95% CI: 0.9–3.9]; difference 10.9%, 95% CI: 7.5–14.8; p < 0.00001). Median event-free survival was longer with pembrolizumab versus placebo (44.4 months, 95% CI: 33.0–not reached vs. 25.3 months, 95% CI: 20.6–33.9; hazard ratio [HR] = 0.81, 95% CI: 0.67–0.99; p = 0.0198) but did not meet the threshold for statistical significance (p = 0.0178). Median overall survival was 60.7 months (95% CI: 51.5–not reached) in the pembrolizumab group versus 58.0 months (95% CI: 41.5–not reached) in the placebo group (HR = 0.90, 95% CI: 0.73–1.12; p = 0.174). Grade 3 or worse adverse events of any cause occurred in 312 of 399 patients (78%) in the pembrolizumab group and 297 of 400 patients (74%) in the placebo group; the most common were nausea (240 [60%] vs. 247 [62%]), anemia (168 [42%] vs. 158 [40%]), and decreased appetite (163 [41%] vs. 172 [43%]). Treatment-related serious adverse events were reported in 102 (26%) and 97 patients (24%). Treatment-related adverse events that led to death occurred in 4 patients (1%) patients in the pembrolizumab group (interstitial ischemia, pneumonia, decreased appetite, and acute kidney injury [n = 1 each]) and 2 patients (< 1%) in the placebo group (neutropenic sepsis and neutropenic colitis [n = 1 each]).

Interpretation: Although neoadjuvant and adjuvant pembrolizumab versus placebo improved the pathological complete response, it did not translate to significant improvement in event-free survival in patients with untreated, locally advanced resectable gastric or gastroesophageal cancer.

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J Clin Oncol. 2024;42(4):410–20

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Perioperative atezolizumab plus fluorouracil, leucovorin, oxaliplatin, and docetaxel for resectable esophagogastric cancer: Interim results from the randomized, multicenter, phase 2/3 DANTE/IKF-s633 trial

Purpose: This trial evaluates the addition of the programmed death-ligand 1 (PD-L1) antibody atezolizumab (ATZ) to standard-of-care fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) as a perioperative treatment for patients with resectable esophagogastric adenocarcinoma (EGA).

Methods: DANTE started as multicenter, randomized phase 2 trial, which was subsequently converted to a phase 3 trial. Here, the authors present the results of the phase 2 proportion, focusing on surgical pathology and safety outcomes on an exploratory basis. Patients with resectable EGA (≥ cT2 or cN+) were assigned to either 4 preoperative and postoperative cycles of FLOT combined with ATZ, followed by 8 cycles of ATZ maintenance (arm A) or FLOT alone (arm B).
Results: 295 patients were randomly assigned (A, 146; B, 149) with balanced baseline characteristics between arms. 23 patients (8%) had tumors with microsatellite instability (MSI), and 58% patients had tumors with a PD-L1 combined positive score (CPS) of ≥ 1. Surgical morbidity (A, 45%; B, 42%) and 60-day mortality (A, 3%; B, 2%) were comparable between arms. Downstaging favored arm A versus arm B (ypT0, 23% vs. 15% [1-sided p = 0.044]; ypT0–T2, 61% vs. 48% [1-sided p = 0.015]; ypN0, 68% vs. 54% [1-sided p = 0.012]). Histopathologic complete regression rates (pathologic complete response or TRG1a) were higher after FLOT plus ATZ (A, 24%; B, 15%; 1-sided p = 0.032), and the difference was more pronounced in the PD-L1 CPS ≥ 10 (A, 33%; B, 12%) and MSI (A, 63%; B, 27%) subpopulations. Complete margin-free (R0) resection rates were relatively high in both arms (A, 96%; B, 95%). The incidence and severity of adverse events were similar in both groups.

Conclusion: Within the limitations of the exploratory nature of the data, the addition of atezolizumab to perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel is safe and improved postoperative stage and histopathologic regression.

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J Clin Oncol. 2024;42(2):146–56

Rau B, Lang H, Koenigsrainer A, Gockel I, Rau HG, Seeliger H, Lerchenmueller C, Reim D, Wahba R, Angele M, Heeg S, Keck T, Weimann A, Topp S, Piso P, Brandl A, Schuele S, Jo P, Pratschke J, Wegel S, Rehders A, Moosmann N, Gaedcke J, Heinemann V, Trips E, Loeffler M, Schlag PM, Thuss-Patience P

Effect of hyperthermic intraperitoneal chemotherapy on cytoreductive surgery in gastric cancer with synchronous peritoneal metastases: The Phase 3 GASTRIPEC-I trial

Purpose: In patients with peritoneal metastasis (PM) from gastric cancer (GC), chemotherapy is the treatment of choice. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are still being debated. This randomized, controlled, open-label, multicenter phase 3 trial explored the impact on overall survival (OS) of HIPEC after CRS.
Patients and methods: Adult patients with GC and histologically proven PM were randomly assigned (1:1) to perioperative chemotherapy and CRS alone (CRS-A) or CRS plus HIPEC (CRS+H). HIPEC comprised mitomycin C 15 mg/m^2 and cisplatin 75 mg/m^2 in 5 liters of saline perfused for 60 minutes at 42 °C. The primary end point was OS; secondary end points included progression-free survival (PFS), other distant metastasis-free survival (MFS), and safety. Analyses followed the intention-to-treat principle.
Results: Between March 2014 and June 2018, 105 patients were randomly assigned (53 patients to CRS-A and 52 patients to CRS+H). The trial stopped prematurely because of slow recruitment. In 55 patients, treatment stopped before CRS mainly due to disease progression/death. Median OS was the same for both groups (CRS+H, 14.9 months [97.2% confidence interval {CI}: 8.7–17.7] vs. CRS-A, 14.9 months [97.2% CI: 7.0–19.4]; p = 0.1647). The PFS was 3.5 months (95% CI: 3.0–7.0) in the CRS-A group and 7.1 months (95% CI: 3.7–10.5; p = 0.047) in the CRS+H group. The CRS+H group showed better MFS (10.2 months [95% CI: 7.7–14.7] vs. CRS-A, 9.2 months [95% CI: 6.8–11.5]; p = 0.0286). The incidence of grade ≥ 3 adverse events was similar between groups (CRS-A, 38.1% vs. CRS+H, 43.6%; p = 0.79).

Conclusion: This study showed no difference in overall survival between cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) (CRS+H) and CRS alone. Progression-free survival and metastasis-free survival were significantly better in the CRS+H group, which needs further exploration. HIPEC did not increase adverse events.

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Global, regional, and national lifetime risks of developing and dying from gastrointestinal cancers in 185 countries: A population-based systematic analysis of GLOBOCAN

Background: Gastrointestinal cancers account for a quarter of the global cancer incidence and a third of cancer-related deaths. The authors sought to estimate the lifetime risks of developing and dying from gastrointestinal cancers at the country, world region, and global levels in 2020.
Methods: For this population-based systematic analysis, they obtained estimates of gastrointestinal cancer incidence and mortality rates from GLOBOCAN for 185 countries, alongside all-cause mortality and population data from the UN. Countries were categorized into quartiles of the Human Development Index (HDI). The lifetime risk of gastrointestinal cancers was estimated with a standard method that adjusts for multiple primaries, taking into account competing risks of death from causes other than cancer and life expectancy.
Findings: The global lifetime risks of developing and dying from gastrointestinal cancers from birth to death was 8.20% (95% confidence interval [CI]: 8.18–8.21) and 6.17% (95% CI: 6.16–6.18) in 2020. For men, the risk of developing gastrointestinal cancers was 9.53% (95% CI: 9.51–9.55) and of dying from them 7.23% (95% CI:

7.22–7.25); for women, the risk of developing gastrointestinal cancers was 6.84% (95% CI: 6.82–6.85) and of dying from them 5.09% (95% CI: 5.08–5.10). Colorectal cancer presented the highest risk, accounting for 38.5% of the total lifetime risk of developing, and 28.2% of dying from, gastrointestinal cancers, followed by cancers of the stomach, liver, esophagus, pancreas, and gallbladder. Eastern Asia has the highest lifetime risks for cancers of the stomach, liver, esophagus, and gallbladder, Australia and New Zealand for colorectal cancer, and Western Europe for pancreatic cancer. The lifetime risk of gastrointestinal cancers increased consistently with increasing level of HDI; however, high HDI countries (the third HDI quartile) had the highest death risk.

Interpretation: The global lifetime risk of gastrointestinal cancers translates to 1 in 12 people developing, and 1 in 16 people dying from, gastrointestinal cancers. The identified high risk and observed disparities across countries warrants context-specific targeted gastrointestinal cancer control and health systems planning.

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Nutrition and Obesity

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Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: The SURMOUNT-4 randomized clinical trial

Importance: The effect of continued treatment with tirzepatide on maintaining initial weight reduction is unknown.
Objective: To assess the effect of tirzepatide, with diet and physical activity, on the maintenance of weight reduction.
Design, setting, and participants: This phase 3, randomized withdrawal clinical trial conducted at 70 sites in 4 countries with a 36-week, open-label tirzepatide lead-in period followed by a 52-week, double-blind, placebo-controlled period included adults with a body mass index ≥ 30 or ≥ 27 and a weight-related complication, excluding diabetes.
Interventions: Participants (n = 783) enrolled in an open-label lead-in period received once-weekly subcutaneous maximum tolerated dose (10 or 15 mg) of tirzepatide for 36 weeks. At week 36, a total of 670 participants were randomized (1:1) to continue receiving tirzepatide (n = 335) or switch to placebo (n = 335) for 52 weeks.
Main outcomes and measures: The primary end point was the mean percent change in weight from week 36 (randomization) to week 88. Key secondary end points included the proportion of participants at week 88 who maintained at least 80% of the weight loss during the lead-in period.
Results: Participants (n = 670; mean age, 48 years; 473 [71%] women; mean weight, 107.3 kg) who completed the 36-week lead-in period experienced a mean weight reduction of 20.9%. The mean percent weight change from week 36 to week 88 was -5.5% with tirzepatide versus 14.0% with placebo (difference, -19.4%; 95% confidence interval: -21.2% to -17.7%; p < 0.001). Overall, 300 participants (89.5%) receiving tirzepatide at 88 weeks maintained at least 80% of the weight loss during the lead-in period compared with 16.6% receiving placebo (p < 0.001). The overall mean weight reduction from week 0 to 88 was 25.3% for tirzepatide and 9.9% for placebo. The most common adverse events were mostly mild to moderate gastrointestinal events, which occurred more commonly with tirzepatide versus placebo.

Conclusions and relevance: In participants with obesity or overweight, withdrawing tirzepatide led to substantial regain of lost weight, whereas continued treatment maintained and augmented initial weight reduction.

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Endoscopy of the Upper GI Tract

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The environmental impact of gastrointestinal procedures: A prospective study of waste generation, energy consumption, and auditing in an endoscopy unit

Background and aims: Gastrointestinal endoscopy procedures are critical for screening, diagnosis, and treatment of a variety of gastrointestinal disorders. However, like the procedures in other medical disciplines, they are a source of environmental waste generation and energy consumption.
Methods: The authors prospectively collected data on total waste generation, energy consumption, and the role of intraprocedural inventory audit of a single tertiary care academic endoscopy unit over a 2-month period (May–June 2022). Detailed data on items used were collected, including procedure type (esophagogastroduodenoscopy or colonoscopy), accessories, intravenous tubing, biopsy jars, linen, and personal protective equipment use. Data on endoscope reprocessing-related waste generation and energy use in the endoscopy unit (equipment, lights, and computers) were also collected. An endoscopy staff-guided auditing and review of the items used during procedures was used to determine potentially recyclable items going to landfill waste.

The waste generated was stratified into biohazardous, non-biohazardous, or potentially recyclable items.
Results: A total of 450 consecutive procedures were analyzed for total waste management (generation and reprocessing) and energy consumption. The total waste generated during the study period was 1398.6 kg (61.6% directly going to landfill, 33.3% biohazard waste, and 5.1% sharps), averaging 3.03 kg/procedure. The average waste directly going to landfill was 219 kg per 100 procedures. The estimated total annual waste generation approximated the size of 2 football fields (1-foot-high layered waste). Endoscope reprocessing generated 194 gallons of liquid waste per day, averaging 13.85 gallons per procedure. Total energy consumption in the endoscopy unit was 277.1 kWh energy per day; for every 100 procedures, amounting to 1200 miles of distance traveled by an average fuel efficiency car. The estimated carbon footprint for every 100 gastrointestinal procedures was 1501 kg carbon dioxide (CO_2) equivalent (= 1680 lbs of coal burned), which would require 1.8 acres of forests to sequester. The recyclable waste audit and review demonstrated that 20% of total waste consisted of potentially recyclable items (8.6 kg/day) that could be avoided by appropriate waste segregation of these items.

Conclusions: On average, every 100 gastrointestinal endoscopy procedures (esophagogastroduodenoscopy/colonoscopy) are associated with 303 kg of solid waste and 1385 gallons of liquid waste generation, and 1980 kWh energy consumption. Potentially recyclable materials account for 20% of the total waste. These data could serve as an actionable model for health systems to reduce total waste generation and decrease landfill waste and water waste toward environmentally sustainable endoscopy units.

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Reducing scope 3 carbon emissions in gastrointestinal endoscopy: Results of the prospective study of the 'Green Endoscopy Project Würzburg'

Objective: Carbon emissions generated by gastrointestinal endoscopy have been recognized as a critical issue. Scope 3 emissions are mainly caused by the manufacturing, packaging and transportation of purchased goods. However, to the authors' knowledge, there are no prospective data on the efficacy of measurements aimed to reduce scope 3 emissions.
Design: The study was performed in a medium-sized academic endoscopy unit. Manufacturers of endoscopic consumables were requested to answer a questionnaire on fabrication, origin, packaging and transport. Based on these data, alternative products were purchased whenever possible. In addition, staff was instructed on how to avoid waste. Thereafter, the carbon footprint of each item purchased was calculated from February to May 2023 (intervention period), and scope 3 emissions were compared with the same period of the previous year (control period).
Results: 26 of 40 companies answered the questionnaire. 229 of 322 products were classified as unfavorable. A switch to alternative items was possible for 47 of 229 items (20.5%). 1666 endoscopies were performed during the intervention period compared with 1751 examinations during the control period (-4.1%). The number of instruments used decreased by 10.0% (3111 vs. 3457). Using fewer and alternative products resulted in 11.5% less carbon emissions (7.09 vs. 8.01 tons of carbon equivalent = tCO_2e). Separation of waste led to a reduction of 20.1% (26.55 vs. 33.24 tCO_2e). In total, carbon emissions could be reduced by 18.4%.

Conclusion: Use of fewer instruments per procedure, recycling packaging material and switching to alternative products can reduce carbon emissions without impairing the endoscopic workflow.

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Endoscopic ultrasonography-guided gastroenterostomy versus uncovered duodenal metal stenting for unresectable malignant gastric outlet obstruction (DRA-GOO): A multicenter randomized controlled trial

Background: Endoscopic ultrasonography-guided gastroenterostomy (EUS-GE) is a novel endoscopic method to palliate malignant gastric outlet obstruction. The aim of this study was to assess whether the use of EUS-GE with a double balloon occluder for malignant gastric outlet obstruction could reduce the need for reintervention within 6 months compared with conventional duodenal stenting.
Methods: An international, multicenter, randomized, controlled trial was conducted at 7 sites in Hong Kong, Belgium, Brazil, India, Italy, and Spain. Consecutive patients (aged ≥ 18 years) with malignant gastric outlet obstruction due to unresectable primary gastroduodenal or pancreatobiliary malignancies, a gastric outlet obstruction score (GOOS) of 0 (indicating an inability in intake food or liquids orally), and an Eastern Cooperative Oncology Group performance status score of 3 or lower were included and randomly allocated (1:1) to receive either EUS-GE or duodenal stenting. The primary outcome was the 6-month reintervention rate, defined as the percentage of patients requiring additional endoscopic intervention due to stent dysfunction (i.e., restenosis of the stent due to tumor ingrowth, tumor overgrowth, or food residue; stent migration; or stent fracture) within 6 months, analyzed in the intention-to-treat

population. Prespecified secondary outcomes were technical success (successful placement of a stent), clinical success (1-point improvement in GOOS within 3 days), adverse events within 30 days, death within 30 days, duration of stent patency, GOOS at 1 month, and quality-of-life scores.
Findings: Between December 1, 2020, and February 28, 2022, 185 patients were screened and 97 (46 men and 51 women) were recruited and randomly allocated (48 to the EUS-GE group and 49 to the duodenal stent group). Mean age was 69.5 years (standard deviation [SD] 12.6) in the EUS-GE group and 64.8 years (SD 13.0) in the duodenal stent group. All randomly allocated patients completed follow-up and were analyzed. Reintervention within 6 months was required in 2 patients (4%) in the EUS-GE group and 14 (29%) in the duodenal stent group ($p = 0.0020$; risk ratio = 0.15; 95% confidence interval [CI]: 0.04–0.61). Stent patency was longer in the EUS-GE group (median not reached in either group; hazard ratio = 0.13; 95% CI: 0.08–0.22; log-rank $p < 0.0001$). 1-month GOOS was significantly better in the EUS-GE group (mean 2.41 [SD 0.7]) than the duodenal stent group (1.91 [SD 0.9], $p = 0.012$). There were no statistically significant differences between the EUS-GE and duodenal stent groups in death within 30 days (10 [21%] vs. 6 [12%] patients, respectively, $p = 0.286$), technical success, clinical success, or quality-of-life scores at 1 month. Adverse events occurred in 11 patients (23%) in the EUS-GE group and in 12 (24%) in the duodenal stent group within 30 days ($p = 1.00$); 3 cases of pneumonia (2 in the EUS-GE group and 1 in the duodenal stent group) were considered to be procedure related.

Interpretation: In patients with malignant gastric outlet obstruction, endoscopic ultrasonography-guided gastroenterostomy can reduce the frequency of reintervention, improve stent patency, and result in better patient-reported eating habits compared with duodenal stenting, and the procedure should be used preferentially over duodenal stenting when expertise and required devices are available.

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Crohn's Disease

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Colombel JF, Sands BE, Gasink C, Yeager B, Adedokun OJ, Izanec J, Ma T, Gao LL, Lee SD, Targan SR, Ghosh S, Hanauer SB, Sandborn WJ

Evolution of symptoms after ustekinumab induction therapy in patients with Crohn's disease

Background and aims: Ustekinumab is an effective treatment of Crohn's disease (CD). Of interest to patients is knowing how soon symptoms may improve. The authors analyzed ustekinumab response dynamics from the ustekinumab CD trials.
Methods: Patients with CD received intravenous induction with ustekinumab approximately 6 mg/kg (n = 458) or placebo (n = 457). Week-8 ustekinumab responders received subcutaneous ustekinumab 90 mg as the first maintenance dose or as an extended induction dose for non-responders. Patient-reported symptom changes (stool frequency, abdominal pain, general well-being) within the first 14 days and clinical outcomes through week 44 were evaluated using the Crohn's Disease Activity Index (CDAI).
Results: After ustekinumab infusion, stool frequency improvement was significantly ($p < 0.05$) greater than placebo on day 1 and for all patient-reported symptoms by day 10. In patients with no history of biologic failure or intolerance, cumulative clinical remission rates increased from 23.0% at week 3 to 55.5% at week 16 after the subcutaneous dose at week 8. Corresponding cumulative rates for patients with a history of biologic failure or intolerance increased from 12.9% to 24.1%. Neither change from baseline in CDAI score nor week-8 ustekinumab pharmacokinetics were associated with week-16 response. Among all patients who received subcutaneous ustekinumab 90 mg every 8 weeks, up to 66.7% were in clinical response at week 44.

Conclusions: Ustekinumab induction provided symptom relief by day 1 post-infusion. Following ustekinumab infusion and a subcutaneous 90 mg injection, clinical outcomes continued to increase through week 16 and up to week 44. Regardless of week 8 clinical status or ustekinumab pharmacokinetics, patients should receive additional treatment at week 8.

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Danese S, Panaccione R, Feagan BG, Afzali A, Rubin DT, Sands BE, Reinisch W, Panés J, Sahoo A, Terry NA, Chan D, Han C, Frustaci ME, Yang Z, Sandborn WJ, Hisamatsu T, Andrews JM, D'Haens GR; GALAXI-1 Study Group

Efficacy and safety of 48 weeks of guselkumab for patients with Crohn's disease: Maintenance results from the phase 2, randomized, double-blind GALAXI-1 trial

Background: Many patients with moderately to severely active Crohn's disease do not respond to available therapies or lose response over time. The GALAXI-1 study previously found that 3 intravenous guselkumab dosages showed superior clinical and endoscopic outcomes over placebo at week 12 in patients with moderately to severely active Crohn's disease. The authors report the safety and efficacy of subcutaneous guselkumab maintenance regimens to week 48 in the GALAXI-1 study.
Methods: They did a phase 2, randomized, multicenter, double-blind trial. Adult patients with moderately to severely active Crohn's disease were randomly allocated with a computer-generated randomization schedule to receive 1 of 5 treatment groups, with regimens consisting

of an intravenous induction phase transitioning to a subcutaneous maintenance phase starting at week 12 in a treat-through design: (1) guselkumab 200→100 mg group (200 mg i.v. at weeks 0, 4, and 8, then 100 mg s.c. every 8 weeks); (2) guselkumab 600→200 mg group (600 mg i.v. at weeks 0, 4, and 8, then 200 mg s.c. every 4 weeks); (3) guselkumab 1200→200 mg group (1200 mg i.v. at weeks 0, 4, and 8, then 200 mg s.c. every 4 weeks); (4) ustekinumab group (approx. 6 mg/kg i.v. at week 0, then 90 mg s.c. every 8 weeks); or (5) placebo group (placebo induction followed by either placebo maintenance [for those with Crohn's Disease Activity Index {CDAI} clinical response at week 12] or crossover to ustekinumab [for those without CDAI clinical response at week 12]). End points assessed at week 48 included CDAI remission (CDAI score < 150), endoscopic response (≥ 50% improvement from baseline in Simple Endoscopic Score for Crohn's Disease [SES-CD] or SES-CD score ≤ 2), and endoscopic remission (SES-CD score ≤ 2) in the primary efficacy analysis population of all randomized patients who received at least 1 dose of study drug, excluding those discontinued during a temporary study pause. Safety analyses included all randomized patients who received at least 1 study drug dose.
Findings: Among 700 patients screened, 309 (112 biologic-naive; 197 biologic-experienced) were included in the primary efficacy analysis population: 61 in the guselkumab 200→100 mg group, 63 in the guselkumab 600→200 mg group, 61 in the guselkumab 1200→200 mg group, 63 in the ustekinumab group, and 61 in the placebo group. 126 (41%) women and 183 (59%) men were included, with median age 36.0 years (interquartile range, 28.0–49.0). At week 48, the numbers of patients with CDAI clinical remission were 39 (64%) in the guselkumab 200→100 mg group, 46 (73%) in the guselkumab 600→200 mg group, 35 (57%) in the guselkumab 1200→200 mg group, and 37 (59%) in the ustekinumab group. The corresponding numbers of patients with endoscopic response were 27 (44%), 29 (46%), 27 (44%), and 19 (30%), respectively, and endoscopic remission was seen in 11 (18%), 11 (17%), 20 (33%), and 4 (6%) patients, respectively. In the placebo group, 15 patients were in CDAI clinical response at week 12 and continued placebo; of these, 9 (60%) were in clinical remission at week 48. 44 patients in the placebo group were not in CDAI clinical response at week 12 and crossed over to ustekinumab; of these, 26 (59%) were in clinical remission at week 48. Up to week 48, adverse events frequencies in the safety population (n = 360) were 46 of 70 patients (66%; 464.9 events per 100 patient-years of follow-up) in the placebo group, 163 of 220 patients (74%; 353.1 per 100 patient-years) in the 3 guselkumab groups combined, and 60 of 71 patients (85%; 350.7 per 100 patient-years) in the ustekinumab group. Among patients treated with guselkumab or ustekinumab, the most frequently reported infections up to week 48 were nasopharyngitis (25/220 guselkumab recipients [11%], 12/114 ustekinumab recipients [11%]) and upper respiratory infections (13 guselkumab recipients [6%], 8 ustekinumab recipients [7%]). After week 12, 1 patient who responded to placebo induction and 2 guselkumab-treated patients had serious infections. No active tuberculosis, opportunistic infections, or deaths occurred.

Interpretation: Patients receiving guselkumab intravenous induction and subcutaneous maintenance treatment achieved high rates of clinical and endoscopic efficacy up to week 48. No new safety concerns were identified.

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Noor NM, Lee JC, Bond S, Dowling F, Brezina B, Patel KV, Ahmad T, Banim PJ, Berrill JW, Cooney R, De La Revilla Negro J, de Silva S, Din S, Durai D, Gordon JN, Irving PM, Johnson M, Kent AJ, Kok KB, Moran GW, Mowat C, Patel P, Probert CS, Raine T, Saich R, Seward A, Sharpstone D, Smith MA, Subramanian S, Upponi SS, Wiles A, Williams HRT, van den Brink GR, Vermeire S, Jairath V, D'Haens GR, McKinney EF, Lyons PA, Lindsay JO, Kennedy NA, Smith KGC, Parkes M; PROFILE Study Group

A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): A multicenter, open-label randomized controlled trial

Background: Management strategies and clinical outcomes vary substantially in patients newly diagnosed with Crohn's disease. The authors evaluated the use of a putative prognostic biomarker to guide therapy by assessing outcomes in patients randomized to either top-down (i.e., early combined immunosuppression with infliximab and immunomodulator) or accelerated step-up (conventional) treatment strategies.
Methods: PROFILE (PRedicting Outcomes For Crohn's dIsease using a moLecular biomarkEr) was a multicenter, open-label, biomarker-stratified, randomized controlled trial that enrolled adults with newly diagnosed active Crohn's disease (Harvey-Bradshaw Index [HBI] ≥ 7, either elevated C-reactive protein [CRP] or fecal calprotectin or both, and endoscopic evidence of active inflammation). Potential participants had blood drawn to be tested for a prognostic biomarker derived from T-cell transcriptional signatures (PredictSURE-IBD assay). Following testing, patients were randomly assigned, via a secure online platform, to top-down or accelerated step-up treatment stratified by biomarker subgroup (IBDhi or IBDlo), endoscopic inflammation (mild, moderate, or severe), and extent (colonic or other). Blinding to biomarker status was maintained throughout the trial. The primary end point was sustained steroid-free and surgery-free remission to week 48. Remission was defined by a composite of symptoms and inflammatory markers at all visits. Flare required active symptoms (HBI ≥ 5) plus raised inflammatory markers (CRP > the upper limit of normal or fecal calprotectin ≥ 200 µg/g, or both), while remission was the converse – i.e., quiescent symptoms (HBI < 5) or resolved inflammatory markers (both CRP ≤ the upper limit of normal and fecal calprotectin < 200 µg/g) or both. Analyses were done in the full analysis (intention-to-treat) population.
Findings: Between December 29, 2017, and January 5, 2022, 386 patients (mean age 33.6 years [standard deviation 13.2]; 179 [46%] female, 207 [54%] male) were randomized: 193 to the top-down group and 193 to the accelerated step-up group. Median time from diagnosis to trial enrolment was 12 days (range 0–191). Primary

outcome data were available for 379 participants (189 in the top-down group; 190 in the accelerated step-up group). There was no biomarker-treatment interaction effect (absolute difference, 1 percentage point, 95% confidence interval [CI]: -15–15; p = 0.944). Sustained steroid-free and surgery-free remission was significantly more frequent in the top-down group than in the accelerated step-up group (149/189 patients [79%] vs. 29/190 patients [15%], absolute difference, 64 percentage points, 95% CI: 57–72; p < 0.0001). There were fewer adverse events (including disease flares) and serious adverse events in the top-down group than in the accelerated step-up group (adverse events: 168 vs. 315; serious adverse events: 15 vs. 42), with fewer complications requiring abdominal surgery (1 vs. 10) and no difference in serious infections (3 vs. 8).

Interpretation: Top-down treatment with combination infliximab plus immunomodulator achieved substantially better outcomes at 1 year than accelerated step-up treatment. The biomarker did not show clinical utility. Top-down treatment should be considered standard of care for patients with newly diagnosed active Crohn's disease.

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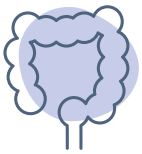

COLON TO RECTUM

Ulcerative Colitis, Crohn's Colitis

Clin Gastroenterol Hepatol. 2024;22(1):135–43.e8

Ward D, Nyboe Andersen N, Gørtz S, Thorn Iversen A, Højgaard Allin K, Beaugerie L, Kirchgesner J, Jess T

Tumor necrosis factor inhibitors in inflammatory bowel disease and risk of immune-mediated inflammatory diseases

Background and aims: Tumor necrosis factor inhibitors (anti-TNF) are effective therapies for several immune-mediated inflammatory diseases (IMIDs). However, case reports have identified the paradoxical occurrence of IMIDs in patients treated with anti-TNF. The authors studied the risk of rheumatoid arthritis, psoriasis, and hidradenitis suppurativa after the initiation of anti-TNF therapy for inflammatory bowel disease (IBD).
Methods: They conducted 2 nationwide cohort studies comprising all patients with IBD in Denmark (2005–2018) and France (2008–2018), and obtained individual-level information on exposure to anti-TNF, diagnoses of IMIDs including rheumatoid arthritis, psoriasis, and hidradenitis suppurativa, and potential confounders from healthcare registers in the respective countries. Cox models were used to estimate hazard ratios (HRs) for the association between anti-TNF exposure and IMIDs and then the estimates from the 2 cohorts were pooled. To test the robustness of the results, an active comparator analysis of anti-TNF monotherapy versus azathioprine monotherapy was performed.
Results: The Danish and French cohorts comprised 18,258 and 88,786 subjects with IBD, respectively, contributing a total of 516,055 person-years of follow-up. Anti-TNF was associated with an increased risk of rheumatoid arthritis, psoriasis, and hidradenitis suppurativa in both the Danish (HR = 1.66; 95% confidence interval [CI]: 1.34–2.07) and the French cohort (HR = 1.78; 95% CI: 1.63–1.94), with a pooled HR of 1.76 (95% CI: 1.63–1.91). Anti-TNF was also associated with an increased risk of the outcomes when compared with azathioprine (pooled HR = 2.94; 95% CI: 2.33–3.70).

Conclusions: In 2 nationwide cohorts of patients with inflammatory bowel disease tumor necrosis factor inhibitor therapy was associated with an increased risk of rheumatoid arthritis, psoriasis, and hidradenitis suppurativa.

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Proton-pump inhibitors and risk of enteric infection in inflammatory bowel disease: A self-controlled case series

Background: The authors tested whether proton-pump inhibitors (PPIs) are associated with enteric infections among those with inflammatory bowel disease (IBD), after adequately accounting for baseline differences between PPI users and non-users.
Methods: This was a self-controlled case series, with each patient serving as their own control. Ambulatory patients with IBD were included if they were tested for enteric infection by multiplex polymerase chain reaction testing panel (GIPCR) and/or Clostridioides difficile toxin PCR from 2015 to 2019 and received PPIs for some but not all of this period. Rates of enteric infections were compared between the PPI-exposed period versus pre- and post-PPI periods identical in duration to the exposed period. Conditional Poisson regression was used to adjust for time-varying factors.
Results: 221 IBD patients were included (49% ulcerative colitis, 46% Crohn's disease, and 5% indeterminate colitis). The median PPI duration was 7 months (interquartile range, 4–11). A total of 25 patients (11%) had a positive GIPCR or C. difficile test in the PPI period, 9 (4%) in the pre-PPI period, and 8 (4%) in the post-PPI period. Observed incidence rates for enteric infections were 2.5, 7.4, and 2.2 per 100 person-years for the pre-PPI, PPI, and post-PPI periods, respectively (adjusted incidence rate ratios = 2.8; 95% confidence interval [CI]: 1.3–6.0 for PPI vs. pre-PPI and 2.9; 95% CI: 1.3–6.4 for PPI vs. post-PPI). The adjusted absolute excess risk associated with PPIs was 4.9 infections per 100 person-years.

Conclusions: Proton-pump inhibitors were associated with a 3-fold increased risk for enteric infection among those with inflammatory bowel disease but had a modest absolute risk.

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Yang Y, Ludvigsson JF, Olén O, Sjölander A, Carrero JJ

Absolute and relative risks of kidney and urological complications in patients with inflammatory bowel disease

Introduction: The burden of kidney and urological complications in patients with inflammatory bowel disease (IBD) remains poorly characterized.
Methods: The authors analyzed association between developing IBD (as a time-varying exposure) and relative risks of receiving diagnoses of chronic kidney disease (CKD), acute kidney injury (AKI), or kidney stones, and experiencing a clinically relevant decline in estimated glomerular filtration rate (eGFR) (CKD progression;

composite of kidney failure or an eGFR decline ≥ 30%) in 1,682,795 individuals seeking healthcare in Stockholm, Sweden, during 2006–2018. They quantified 5- and 10-year absolute risks of these complications in a parallel matched cohort of IBD cases and random controls matched (1:5) on sex, age, and eGFR.
Results: During median 9 years, 10,117 participants developed IBD. Incident IBD was associated with higher risks of kidney-related complications compared with non-IBD periods: hazard ratio (HR) was 1.24 (95% confidence interval [CI]: 1.10–1.40) for receiving a CKD diagnosis and 1.11 (95% CI: 1.00–1.24) for CKD progression. For absolute risks, 11.8% IBD cases had a CKD event within 10 years. Of these, 6.4% received a CKD diagnosis, and 7.9% reached CKD progression. The risks of AKI (HR = 1.97 [95% CI: 1.70–2.29]; 10-year absolute risk 3.6%) and kidney stones (HR = 1.69 [95% CI: 1.48–1.93]; 10-year absolute risk 5.6%) were also elevated. Risks were similar in Crohn's disease and ulcerative colitis.

Discussion: More than 10% of patients with inflammatory bowel disease (IBD) developed chronic kidney disease within 10 years from diagnosis, with many not being identified through diagnostic codes. This, together with elevated acute kidney injury and kidney stone risks, highlights the need of established protocols for kidney function monitoring and referral to nephrological/urological care for patients with IBD.

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Ben-Horin S, Salomon N, Karampekos G, Viazis N, Lahat A, Ungar B, Eliakim R, Kuperstein R, Kriger-Sharabi O, Reiss-Mintz H, Yanai H, Dotan I, Zittan E, Maharshak N, Hirsch A, Weitman M, Mantzaris GJ, Kopylov U

Curcumin-QingDai combination for patients with active ulcerative colitis: A randomized, double-blinded, placebo-controlled trial

Background and aims: The authors evaluated the efficacy of herbal combination of curcumin-QingDai (CurQD) in active ulcerative colitis (UC).
Methods: Part I was an open-label trial of CurQD in patients with active UC, defined by a Simple Clinical Colitis Activity Index (SCCAI) score ≥ 5 and a Mayo endoscopic subscore (MES) ≥ 2. Part II was a placebo-controlled trial conducted in Israel and Greece, randomizing active UC patients at a 2:1 ratio to enteric-coated CurQD 3 g/day or placebo for 8 weeks. The coprimary outcome was clinical response (reduction in the SCCAI of ≥ 3 points) and an objective response (MES improvement of ≥ 1 or a 50% fecal calprotectin reduction). Responding patients continued either maintenance curcumin or placebo alone for an additional 8 weeks. Aryl-hydrocarbon receptor activation was assessed by cytochrome P450 1A1 (CYP1A1) mucosal expression.
Results: In part I, 7 of 10 patients responded and 3 of 10 achieved clinical remission. Of 42 patients in part II, the week-8 coprimary outcome was achieved in 43% and 8% of CurQD and placebo patients, respectively (p = 0.033). Clinical response was observed in 85.7% versus 30.7% (p < 0.001), clinical remission in 14 of 28 (50%) versus 1 of 13 (8%; p = 0.01), a 50% calprotectin reduction in 46.4% versus 15.4% (p = 0.08), and endoscopic improvement in 75% versus 20% (p = 0.036) in the CurQD and placebo groups, respectively. Adverse events were comparable between groups. By week 16, curcumin-maintained clinical response, clinical remission, and clinical biomarker response rates were 93%, 80%, and 40%, respectively. CurQD uniquely up-regulated mucosal CYP1A1 expression, which was not observed among patients receiving placebo, mesalamine, or biologics.

Conclusions: In this placebo-controlled trial, curcumin-QingDai was effective for inducing response and remission in active ulcerative colitis (UC) patients. The aryl-hydrocarbon receptor pathway may merit further study as a potential UC treatment target.

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Outcome of biological therapies and small molecules in ulcerative proctitis: A Belgian multicenter cohort study

Background and aims: Several advanced therapies (biologic therapies and small molecules) have been approved for the treatment of moderate-to-severe ulcerative colitis. The registration trials for these agents typically excluded patients with isolated proctitis, leaving an evidence gap. The authors evaluated efficacy and safety of advanced therapies in patients with ulcerative proctitis (UP).
Methods: This multicenter retrospective cohort study included consecutive patients with active UP (Mayo endoscopy subscore ≥ 2, rectal inflammation up to 15 cm) initiating advanced therapy, after failing conventional therapy. The primary end point was short-term steroid-free clinical remission (total Mayo score ≤ 2 with no individual subscore > 1). In addition, drug persistence and relapse-free and colectomy-free survival were assessed. Both binary logistic and Cox regression analyses were performed.
Results: In total, 167 consecutive patients (52.0% female; median age 41.0 years; 82.0% bionaive) underwent 223 courses of therapy for UP (38 adalimumab, 14 golimumab, 54 infliximab, 9 ustekinumab, 99 vedolizumab, 9 tofacitinib). The primary end point was achieved with 36.3% of the treatment courses, and based on multivariate analysis, more commonly attained in bionaive patients (p = 0.001), patients treated with vedolizumab (p = 0.001), patients with moderate endoscopic disease activity (p = 0.002), and a body mass index < 25 kg/m^2

(p = 0.018). Drug persistence was significantly higher in patients treated with vedolizumab (p < 0.001) and patients with a shorter disease duration (p = 0.006). No new safety signals were observed.

Conclusions: Advanced therapies are also efficacious and safe in patients with ulcerative colitis limited to the rectum. Therefore, the inclusion of patients with ulcerative proctitis in future randomized-controlled trials should be considered.

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Hormonal contraceptives reduce active symptomatic disease but may increase intestinal inflammation in IBD

Background: Among women of reproductive age with inflammatory bowel disease (IBD), the authors aimed to assess the relationship of hormonal contraceptives (HCs) with IBD-related symptoms, and intestinal inflammation.
Methods: A nested cohort of women in the longitudinal Manitoba Living with IBD Study, ages 18 to 49, were followed for 1 year, with bi-weekly online surveys. This included a validated measure of disease activity; IBD Symptom Inventory (IBDSI), and stool samples obtained at 3 time-points for assessment of fecal calprotectin (FC). Use of HC included oral and vaginal intrauterine devices. Logistic regression analysis was used to assess the association between HC and IBD-related symptoms (IBDSI > 14 for Crohn's disease, > 13 for ulcerative colitis), or inflammation (FC > 250 µg/g) at any measurement point in the study.
Results: Of 71 women, 17 (24%) reported taking HC in the 1-year period. Adjusting for age, disease type, disease duration, and smoking status, the odds of having increased IBD-related symptoms (IBDSI) during the year were lower for women using HC compared with women not using HC (adjusted odds ratio [aOR] = 0.16, 95% confidence interval [CI]: 0.02–0.90). Conversely, women using HC were more likely to have inflammation during the year (aOR = 5.7, 95% CI: 1.23–43.6).

Conclusions: Hormonal contraceptive (HC) use among women with inflammatory bowel disease (IBD) was associated with a lower likelihood of IBD-related symptoms but a higher likelihood of experiencing intestinal inflammation (fecal calprotectin > 250 µg/g) over 1 year. Further work is needed to examine this dichotomous result, potentially examining aspects such as duration of HC use, and the types of HC.

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Milo F, Imondi C, D'Amore C, Angelino G, Knafelz D, Bracci F, Dall'Oglio L, De Angelis P, Tabarini P

Short-term psychodynamic psychotherapy in addition to standard medical therapy increases clinical remission in adolescents and young adults with inflammatory bowel disease: A randomized controlled trial

Background: Inflammatory bowel diseases (IBD) are chronic and pervasive conditions of the gastrointestinal tract with a rising incidence in pediatric and young adult populations. Evidence suggests that psychological disorders might be associated with relapse of disease activity. This study aims to evaluate the efficacy of short-term psychodynamic psychotherapy (STPP) in addition to standard medical therapy (SMT) in maintaining clinical remission in adolescents and young adults (AYA) with quiescent IBD, compared with SMT alone.
Methods: A 2-arm, single-center, randomized, controlled trial was conducted in 60 IBD AYA in clinical remission. Patients were randomized to receive an 8-week STPP+SMT (n = 30) or SMT alone (n = 30). The primary outcome was the steroid-free remission rate at 52 weeks after treatment. Secondary outcomes included the overall hospitalization rate within 52 weeks after treatment, and medication adherence obtained from patient's electronic medical records.
Results: Intention-to-treat analysis showed significant improvement in maintaining disease remission rates in the 8-week STPP+SMT group compared with the control group. The proportion of patients maintaining steroid-free remission at 52 weeks was higher in patients in the STPP+SMT group (93.1%) compared with patients randomized to the control group (64.3%; p = 0.01). There were no significant differences in secondary outcomes, except for depression reduction in the STPP+SMT group.

Conclusions: An 8-week short-term psychodynamic psychotherapy intervention in addition to standard medical therapy effectively increases the steroid-free remission rates in adolescents and young adults with quiescent inflammatory bowel disease. Results do not support effects for other secondary outcomes, except for depression reduction.

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Gupta A, Peyrin-Biroulet L, Ananthakrishnan AN

Risk of cancer recurrence in patients with immune-mediated diseases with use of immunosuppressive therapies: An updated systematic review and meta-analysis

Background and aims: There are limited data on the safety of immunosuppressive therapy use in individuals with immune-mediated diseases with a history of

malignancy, particularly with newer biologic and small-molecule treatments.
Methods: The authors performed a systematic search of PubMed and Embase databases to identify studies examining the impact of immunosuppressive therapies on cancer recurrence across several immune-mediated diseases. Studies were pooled together using random-effects meta-analysis and stratified by type of treatment. Primary outcome was occurrence of incident cancers, defined as new or recurrent.
Results: The meta-analysis included 31 studies (17 inflammatory bowel disease, 14 rheumatoid arthritis, 2 psoriasis, and 1 ankylosing spondylitis) contributing 24,328 persons and 85,784 person-years (PY) of follow-up evaluation. Rates of cancer recurrence were similar among individuals not on immunosuppression (1627 incident cancers, 43,765 PY; 35 per 1000 PY; 95% confidence interval [CI]: 27–43), receiving an anti-tumor necrosis factor (571 incident cancers, 17,772 PY; 32 per 1000 PY; 95% CI: 25–38), immunomodulators (1104 incident cancers, 17,018 PY; 46 per 1000 PY; 95% CI: 31–61), combination immunosuppression (179 incident cancers, 2659 PY; 56 per 1000 PY; 95% CI: 31–81). Patients receiving ustekinumab (5 incident cancers, 213 PY; 21 per 1000 PY; 95% CI: 0–44) and vedolizumab (37 incident cancers, 1951 PY; 16 per 1000 PY; 95% CI: 5–26) had numerically lower rates of cancer. There were no studies on Janus kinase inhibitors. Stratification of studies by timing of immunosuppression initiation did not reveal a medication effect based on early (< 5 years) or delayed treatment initiation.

Conclusions: In patients with immune-mediated diseases and a history of malignancy, similar rates of cancer recurrence were observed in those on no immunosuppression compared with different immunosuppressive treatments.

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Inflamm Bowel Dis. 2024;30(2):159–66

Yerushalmy-Feler A, Olbjorn C, Kolho KL, Aloi M, Musto F, Martin-de-Carpi J, Lozano-Ruf A, Yogev D, Matar M, Scarallo L, Bramuzzo M, de Ridder L, Kang B, Norden C, Wilson DC, Tzivinikos C, Turner D, Cohen S

Dual biologic or small molecule therapy in refractory pediatric inflammatory bowel disease (DOUBLE-PIBD): A multicenter study from the Pediatric IBD Porto Group of ESPGHAN

Background: Current data on dual biologic therapy in children are limited. This multicenter study aimed to evaluate the effectiveness and safety of dual therapy in pediatric patients with inflammatory bowel disease (IBD).
Methods: A retrospective study from 14 centers affiliated with the Pediatric IBD Interest and Porto Groups of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). Included were children with IBD who underwent combinations of biologic agents or biologic and small molecule therapy for at least 3 months. Demographic, clinical, laboratory, endoscopic, and imaging data were collected. Adverse events were recorded.
Results: 62 children (35 Crohn's disease, 27 ulcerative colitis; median age 15.5 years [interquartile range, 13.1–16.8]) were included. They had all failed previous biologic therapies, and 47 (76%) failed at least 2 biologic agents. The dual therapy included an anti-tumor necrosis factor agent and vedolizumab in 30 children (48%), anti-tumor necrosis factor and ustekinumab in 21 children (34%), vedolizumab and ustekinumab in 8 children (13%), and tofacitinib with a biologic in 3 children (5%). Clinical remission was observed in 21 (35%), 30 (50%), and 38 (63%) children at 3, 6, and 12 months, respectively. Normalization of C-reactive protein and decrease in fecal calprotectin to < 250 µg/g were achieved in 75% and 64%, respectively, at 12 months of follow-up. 29 children (47%) sustained adverse events, 8 of which were regarded as serious and led to discontinuation of therapy in 6.

Conclusions: Dual biologic therapy may be effective in children with refractory inflammatory bowel disease. The potential efficacy should be weighed against the risk of serious adverse events.

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Caenepeel C, Falony G, Machiels K, Verstockt B, Goncalves PJ, Ferrante M, Sabino J, Raes J, Vieira-Silva S, Vermeire S

Dysbiosis and associated stool features improve prediction of response to biological therapy in inflammatory bowel disease

Background and aims: Dysbiosis of the gut microbiota is considered a key contributor to inflammatory bowel disease (IBD) etiology. Here, the authors investigated potential associations between microbiota composition and the outcomes to biological therapies.
Methods: The study prospectively recruited 296 patients with active IBD (203 with Crohn's disease, 93 with ulcerative colitis) initiating biological therapy. Quantitative microbiome profiles of pretreatment and posttreatment fecal samples were obtained combining flow cytometry with 16S amplicon sequencing. Therapeutic response was assessed by endoscopy, patient-reported outcomes, and changes in fecal calprotectin. The effect of therapy on microbiome variation was evaluated using constrained ordination methods. Prediction of therapy outcome was performed using logistic regression with 5-fold cross-validation.
Results: At baseline, 65.9% of patients carried the dysbiotic Bacteroides2 (Bact2) enterotype, with a significantly higher prevalence among patients with ileal involvement (76.8%). Microbiome variation was associated with the choice of biological therapy rather than with therapeutic outcome. Only anti-tumor necrosis

factor-α treatment resulted in a microbiome shift away from Bact2, concomitant with an increase in microbial load and butyrogen abundances and a decrease in potentially opportunistic Veillonella. Remission rates for patients hosting Bact2 at baseline were significantly higher with anti-tumor necrosis factor-α than with vedolizumab (65.1% vs. 35.2%). A prediction model, based on anthropometrics and clinical data, stool features (microbial load, moisture, and calprotectin), and Bact2 detection predicted treatment outcome with 73.9% accuracy for specific biological therapies.

Conclusion: Fecal characterization based on microbial load, moisture content, calprotectin concentration, and enterotyping may aid in the therapeutic choice of biological therapy in inflammatory bowel disease.

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J Crohns Colitis. 2024;18(2):192–203

Ranjan MK, Kumar P, Vuyyuru SK, Kante B, Mundhra SK, Golla R, Virmani S, Sharma R, Sahni P, Das P, Kalaivani M, Upadhyay AD, Makharia G, Kedia S, Ahuja V

Thiopurines have sustained long-term effectiveness in patients with inflammatory bowel disease, which is independent of disease duration at initiation: A propensity score matched analysis

Background and aims: Thiopurines are viable option for the treatment of inflammatory bowel disease (IBD) in resource-limited countries. However, data on the effect of disease duration at thiopurines initiation on long-term effectiveness are limited.
Method: The authors performed a propensity matched analysis of a retrospective cohort of patients with ulcerative colitis (UC) and Crohn's disease (CD). Patients initiated on thiopurines early in the disease course (≤ 2 years) were compared with those started late (> 2 years). Effectiveness was defined as no requirement for hospitalization, anti-tumor necrosis factor (TNF) agents, or surgery, and minimum steroid requirement (≤ 1 steroid course in 2 years) during follow-up.
Results: A total of 988 patients (UC: 720, CD: 268) were included (male: 665 [60.8%], median age: 40 [32–51] years, median follow-up: 40 [19–81] months). Overall effectiveness at 5 and 10 years was 79% and 72% in UC, and 69% and 63% in CD, respectively. After propensity score matching, there was no difference in 5- and 10-year effectiveness between early and late thiopurine initiation groups either for UC (81% and 80% vs. 82% and 74%; p = 0.92) or CD (76% and 66% vs. 72% and 51%, p = 0.32). Male sex for UC (negative: hazard ratio [HR] = 0.67, 95% confidence interval [CI]: 0.45–0.97; p = 0.03), and ileal involvement (positive: HR = 3.03, 95% CI: 1.32–6.71; p = 0.008), steroid-dependent disease (positive: HR = 2.70, 95% CI: 1.26–5.68; p = 0.01) and adverse events (negative: HR = 0.47, 95% CI: 0.27–0.80; p = 0.005) for CD were predictors of thiopurine effectiveness.

Conclusion: Thiopurines have sustained long-term effectiveness in both ulcerative colitis and Crohn's disease. However, early thiopurine initiation had no better effect on long-term disease outcome compared with late initiation.

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IBS, Functional and Motility Disorders

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Decraecker L, De Looze D, Hirsch DP, De Schepper H, Arts J, Caenepeel P, Bredenoord AJ, Kolkman J, Bellens K, Van Beek K, Pia F, Peetermans W, Vanuytsel T, Denadai-Souza A, Belmans A, Boeckxstaens G

Treatment of non-constipated irritable bowel syndrome with the histamine 1 receptor antagonist ebastine: A randomized, double-blind, placebo-controlled trial

Objective: The authors evaluated the histamine 1 receptor antagonist ebastine as a potential treatment for patients with non-constipated irritable bowel syndrome (IBS) in a randomized, placebo-controlled phase 2 study.
Methods: Non-constipated patients with IBS fulfilling the Rome III criteria were randomly assigned to 20 mg ebastine or placebo for 12 weeks. Subjects scored global relief of symptoms (GRS) and abdominal pain intensity (API). A subject was considered a weekly responder for GRS if total or obvious relief was reported and a responder for API if the weekly average pain score was reduced by at least 30% versus baseline. The primary end points were the proportion of subjects who were weekly responders for at least 6 out of the 12 treatment weeks for both GRS and API ('GRS+API', composite end point) and for GRS and API separately.
Results: 202 participants (32 ± 11 years, 68% female) were randomly allocated to receive ebastine (n = 101) or placebo (n = 101). Treatment with ebastine resulted in significantly more responders (12%, 12/92) for GRS+API compared with placebo (4%, 4/87, p = 0.047) while the proportion of responders for GRS and API separately was higher for ebastine compared with placebo, although not statistically significant (placebo vs. ebastine, GRS: 7% [6/87] vs. 15% [14/91], p = 0.072; API: 25% [20/85] vs. 37% [34/92], p = 0.081).

Conclusions: This study shows that ebastine is superior to placebo and should be further evaluated as novel treatment for patients with non-constipated irritable bowel syndrome.

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Di Lorenzo C, Khlevner J, Rodriguez-Araujo G, Xie W, Huh SY, Ando M, Hyams JS, Nurko S, Benninga MA, Simon M, Hewson ME, Saps M

Efficacy and safety of linaclotide in treating functional constipation in pediatric patients: A randomized, double-blind, placebo-controlled, multicenter, phase 3 trial

Background: Linaclotide, a guanylate cyclase C agonist, has been approved in the USA for the treatment of chronic idiopathic constipation and irritable bowel syndrome with predominant constipation in adults. The authors aimed to assess the efficacy and safety of linaclotide in pediatric patients aged 6–17 years with functional constipation.
Methods: This randomized, double-blind, placebo-controlled, multicenter, phase 3 study was done at 64 clinic or hospital sites in 7 countries (USA, Canada, Israel, Italy, the Netherlands, Ukraine, and Estonia). Patients aged 6–17 years who met modified Rome III criteria for functional constipation were randomly assigned (1:1), with a block size of 4 and stratified by age (6–11 years and 12–17 years), to receive either oral linaclotide 72 µg or placebo once daily for 12 weeks. Participants, investigators, and data assessors were masked to assignment. The primary efficacy end point was change from baseline (CFB) in the 12-week frequency rate of spontaneous bowel movements (SBMs; occurring in the absence of rescue medication on the calendar day of or before the bowel movement) per week and the secondary efficacy end point was CFB in stool consistency over the 12-week treatment period; efficacy and safety were analyzed in all patients in the randomized population who received at least 1 dose of study intervention (modified intention-to-treat population and safety population, respectively).
Findings: Between October 1, 2019, and March 21, 2022, 330 patients were enrolled and randomly assigned to linaclotide (n = 166) or placebo (n = 164). Two patients in the linaclotide group did not receive any treatment; thus, efficacy and safety end points were assessed in 328 patients (164 patients in each group). 293 patients (89%) completed the 12-week treatment period (148 in the linaclotide group and 145 in the placebo group). 181 of 328 patients (55%) were female and 147 (45%) were male. At baseline, the mean frequency rate for SBMs was 1.28 SBMs per week (standard deviation [SD] 0.87) for placebo and 1.16 SBMs per week (SD 0.83) for linaclotide, increasing to 2.29 SBMs per week (SD 1.99) for placebo and 3.41 SBMs per week (SD 2.76) for linaclotide during intervention. Compared with placebo (least-squares mean [LSM] CFB 1.05 SBMs per week [standard error [SE] 0.19]), patients treated with linaclotide showed significant improvement in SBM frequency (LSM CFB 2.22 SBMs per week [SE 0.19]; LSM CFB difference 1.17 SBMs per week [95% confidence interval {CI}: 0.65–1.69]; p < 0.0001). Linaclotide also significantly improved stool consistency over placebo (LSM CFB 1.11 [SE 0.08] vs. 0.69 [SE 0.08]; LSM CFB difference 0.42 [95% CI: 0.21–0.64]; p = 0.0001). The most reported treatment-emergent adverse event (TEAE) by patients treated with linaclotide was diarrhea (7/164 [4%] vs. 3/164 patients [2%] in the placebo group) and by patients treated with placebo was COVID-19 (5 [3%] vs. 4 [2%] in the linaclotide group). The most frequent treatment-related TEAE was diarrhea (linaclotide: 6 patients [4%]; placebo: 2 patients [1%]). One serious adverse event of special interest (treatment-related severe diarrhea resulting in dehydration and hospitalization) occurred in a female patient aged 17 years in the linaclotide group; this case resolved without sequelae after administration of intravenous fluids. No deaths occurred during the study.

Interpretation: Linaclotide is an efficacious and well tolerated treatment for functional constipation in pediatric patients and has subsequently been approved by the US Food and Drug Administration for this indication.

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Colorectal Cancer Screening/ Endoscopy

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Wisse PHA, de Klaver W, van Wifferen F, van Maaren-Meijer FG, van Ingen HE, Meiqari L, Huitink I, Bierkens M, Lemmens M, Greuter MJE, van Leerdam ME, Spaander MCW, Dekker E, Coupé VMH, Carvalho B, de Wit M, Meijer GA

The multitarget fecal immunochemical test for improving stool-based colorectal cancer screening programs: A Dutch population-based, paired-design, intervention study

Background: The fecal immunochemical test (FIT) is widely employed for colorectal cancer (CRC) screening. However, its sensitivity for advanced precursor lesions remains suboptimal. The multitarget FIT (mtFIT), measuring hemoglobin, calprotectin, and serpin family F member 2, has demonstrated enhanced sensitivity for advanced neoplasia, especially advanced adenomas, at equal specificity to FIT. This study aimed to prospectively validate and investigate the clinical utility of mtFIT versus FIT in a setting of population-based CRC screening.
Methods: Individuals aged 55–75 years and who were eligible for the Dutch national FIT-based CRC screening program were invited to submit both a FIT and mtFIT sample collected from the same bowel movement. Positive FIT (47 µg/g hemoglobin cut-off) or mtFIT (based on decision-tree algorithm) led to a colonoscopy referral. The primary outcome was the relative detection rate of mtFIT versus FIT for all advanced neoplasia. Secondary outcomes were the relative detection rates of CRC, advanced adenoma, and advanced serrated polyps individually and the long-term effect of mtFIT-based versus FIT-based programmatic screening on CRC incidence, mortality, and cost, determined with microsimulation modelling.
Findings: Between March 25 and December 7, 2022, 35,786 individuals were invited to participate in the

study, of whom 15,283 (42.7%) consented, and 13,187 of 15,283 (86.3%) provided both mtFIT and FIT samples with valid results. Of the 13,187 participants, 6637 (50.3%) were male and 6550 (49.7%) were female. mtFIT showed a 9.11% (95% confidence interval [CI]: 8.62–9.61) positivity rate and a 2.27% (95% CI: 2.02–2.54) detection rate for advanced neoplasia, compared with a positivity rate of 4.08% (95% CI: 3.75–4.43) and a detection rate of 1.21% (95% CI: 1.03–1.41) for FIT. Detection rates of mtFIT versus FIT were 0.20% (95% CI: 0.13–0.29) versus 0.17% (95% CI: 0.11–0.27) for CRC; 1.64% (95% CI: 1.43–1.87) versus 0.86% (95% CI: 0.72–1.04) for advanced adenoma, and 0.43% (95% CI: 0.33–0.56) versus 0.17% (95% CI: 0.11–0.26) for advanced serrated polyps. Modelling demonstrated that mtFIT-based screening could reduce CRC incidence by 21% and associated mortality by 18% compared with the current Dutch CRC screening program, at feasible costs. Furthermore, at equal positivity rates, mtFIT outperformed FIT in terms of diagnostic yield. At an equally low positivity rate, mtFIT-based screening was predicted to further decrease CRC incidence by 5% and associated mortality by 4% compared with FIT-based screening.

Interpretation: The higher detection rate of multitarget fecal immunochemical test (mtFIT) for advanced adenoma compared with FIT holds the potential to translate into additional and clinically meaningful long-term colorectal cancer (CRC) incidence and associated mortality reductions in programmatic CRC screening.

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Rex DK, Haber GB, Khashab M, Rastogi A, Hasan MK, DiMaio CJ, Kumta NA, Nagula S, Gordon S, Al-Kawas F, Waye JD, Razjouyan H, Dye CE, Moyer MT, Shultz J, Lahr RE, Yuen PYS, Dixon R, Boyd L, Pohl H

Snare tip soft coagulation vs. argon plasma coagulation vs. no margin treatment after large non-pedunculated colorectal polyp resection: A randomized trial

Background and aims: Thermal treatment of the defect margin after endoscopic mucosal resection (EMR) of large non-pedunculated colorectal lesions reduces the recurrence rate. Both snare tip soft coagulation (STSC) and argon plasma coagulation (APC) have been used for thermal margin treatment, but there are few data directly comparing STSC with APC for this indication.
Methods: The authors performed a randomized 3-arm trial in 9 US centers comparing STSC with APC with no margin treatment (control) of defects after EMR of colorectal non-pedunculated lesions ≥ 15 mm. The primary end point was the presence of residual lesion at first follow-up.
Results: There were 384 patients and 414 lesions randomized, and 308 patients (80.2%) with 328 lesions completed ≥ 1 follow-up. The proportion of lesions with residual polyp at first follow-up was 4.6% with STSC, 9.3% with APC, and 21.4% with control subjects (no margin treatment). The odds of residual polyp at first follow-up were lower for STSC and APC when compared with control subjects ($p = 0.001$ and $p = 0.01$, respectively). The difference in odds was not significant between STSC and APC. STSC took less time to apply than APC (median, 3.35 vs. 4.08 minutes; $p = 0.019$). Adverse event rates were low, with no difference between arms.

Conclusions: In a randomized trial snare tip soft coagulation (STSC) and argon plasma coagulation (APC) were each superior to no thermal margin treatment after endoscopic mucosal resection (EMR). STSC was faster to apply than APC. Because STSC also results in lower cost and plastic waste than APC (APC requires an additional device), this study supports STSC as the preferred thermal margin treatment after colorectal EMR.

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Gastrointestinal Infections, Diverticular Disease, Other Inflammation

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Spartz EJ, DeDecker LC, Fansiwala KM, Noorian S, Roney AR, Hakimian S, Sauk JS, Chen PH, Limketkai BN

Recent trends and risk factors associated with Clostridioides difficile infections in hospitalized patients with inflammatory bowel disease

Background: Clostridioides difficile infections (CDIs) are common among patients with inflammatory bowel disease (IBD) and can mimic and exacerbate IBD flares, thus warranting appropriate testing during flares.
Aims: To examine recent trends in rates of CDI and associated risk factors in hospitalized IBD patients, which may better inform targeted interventions to mitigate the risk of infection.
Methods: This is a retrospective analysis using the Nationwide Readmissions Database from 2010 to 2020 of hospitalized individuals with Crohn's disease (CD) or ulcerative colitis (UC). Longitudinal changes in rates of CDI were evaluated using International Classification of Diseases codes. Multivariable logistic regression evaluated the association between patient- and hospital-related factors and CDI.
Results: There were 2,521,935 individuals with IBD who were hospitalized at least once during the study period. Rates of CDI in IBD-related hospitalizations increased from 2010 to 2015 (CD: 1.64–3.32%, $p < 0.001$; UC: 4.15–5.81%, $p < 0.001$), followed by a steady decline from 2016 to 2020 (CD: 3.15–2.27%, $p < 0.001$; UC: 5.04–4.27%, $p < 0.001$). In multivariable models, CDI was associated with the Charlson-Deyo comorbidity index, public insurance, and hospital size. CDI was associated with increased mortality.

Conclusions: Rates of Clostridioides difficile infection (CDI) among hospitalized patients with inflammatory bowel disease (IBD) had initially increased, but have declined since 2015. Increased comorbidity, large hospital size, public insurance, and urban teaching hospitals were associated with higher rates of CDI. CDI was associated with increased mortality in hospitalized patients with IBD. Continued vigilance, infection control, and treatment of CDI can help continue the trend of declining infection rates.

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AI in gastroenterology

"Deep learning" means time and cost savings in gastroenterology

Machine learning may also play an important role in benign diseases in the future

By Dr. Corinna Kolac

Several developments were needed before artificial intelligence (AI) could become established in gastroenterology. Thanks to "deep learning", a step forward in AI, machine learning has been part of gastroenterology for some 10 years now. New applications are being added almost daily. The time was ripe for international experts to exchange their thoughts at the Falk Foundation e.V. workshop on March 14, 2024 in Copenhagen. In the future, AI will be able to help diagnose not only malignant diseases but also benign diseases of the gastrointestinal tract (GIT), specifically eosinophilic esophagitis (EoE), gastroesophageal reflux disease (GERD), achalasia and inflammatory bowel disease, as well as documenting treatment outcomes.

Artificial intelligence: although this term has been used for more than 30 years, opportunities involving AI have recently multiplied and advanced tremendously. While many people still tend to understand it as an expert-based "symbolic AI", machine learning (ML) – in its classic form or in the form of "deep learning" – has made real improvements possible in gastroenterology which wouldn't have happened otherwise. The differences are considerable. Symbolic or knowledge-based AI involves logical applications trained using expert knowledge. AI arrives at its deductions based on a series of variables. One good example of this – an entirely non-medical one – is the chess computer, which has internalized the rules of the game and makes decisions using these rules. As **Prof. Jakob N. Kather**, Dresden (Germany), explained, ML makes use of a different philosophy. Initially, no expert knowledge is made available. The machine receives examples such as endoscopic images and recognizes commonalities and differences. While in classic ML only a few model parameters are processed, "deep learning" can involve consideration of millions of parameters.

Machine learning can be unsettling

The machine itself becomes an expert through examples – an idea that is oftentimes unsettling. The question arises as to how trustworthy diagnoses which are generated by an AI can be. This requires a determination of the uncertainty in ML, explained **Prof. Christoph Palm**, Regensburg (Germany). AI, too, can make mistakes. A good assessment of the uncertainty of results generated by AI can help to identify problematic result outputs and define the need for human intervention. One major uncertainty lies, for example, in the data made available. **Dr. Sravanthi Parasa**, Seattle (USA), gave a presentation on this subject. Thus, an AI can only be used universally if it is equipped with images from different clinics collected worldwide. All ethnicities should be taken into account. In principle, an AI is first "fed" a large number of images and object descriptions. The acquired knowledge is then tested using additional images. Only then is it validated with images of unknown content. The images must be of high quality. It is also important that there are no imbalances, for instance, if the AI has been trained with too many images of healthy test subjects compared to images of abnormal findings.

Use of AI for benign diseases

Dr. Alanna Ebigbo, Augsburg (Germany), considers the use of ML useful for various benign diseases such as EoE. The criteria for EoE are often not entirely clear to clinicians. Edema, rings, exudate, furrows and strictures – awareness about the disease still needs to be raised [1]. AI could provide valuable services here. A preclinical study has already been able to show the usefulness of AI in diagnosing EoE [2]. A Japanese research group even demonstrated that their AI-assisted diagnostic system was able to distinguish between healthy individuals, EoE patients and images of patients with esophageal candidiasis [3]. From a clinical perspective, AI is capable of detecting EoE. An AI-supported reporting system is also conceivable. AI could make EoE diagnostics more efficient. Preclinical results on the use of AI in GERD are also available. It has been shown that AI is superior in accuracy to university graduates in the classification of GERD [4]. As Dr. Ebigbo emphasized, AI is always a significant option when expertise is lacking in a particular field. For example, evaluating the results of high-resolution esophageal manometry in achalasia is always a challenge. AI has shown a high level of precision in this area [5]. Meanwhile, AI has become very important in the functional diagnosis of benign diseases. The results can be interpreted quickly and easily and AI provides training for future experts. It can influence the clinical decision during endoscopy and can be particularly helpful – like a second opinion – in cases that are difficult to assess.
Prof. Raf Bisschops, Leuven (Belgium), highlighted the importance of AI with regard to inflammatory bowel disease, especially with regard to ulcerative colitis. He emphasized the difficulties involved in differentiating degrees of severity, for which various scores (e.g. Mayo, UCEIS) are available. In the past, the different classifications have already led to patients being excluded from studies. This problem could be circumvented with the help of AI. Initial AI developments have already

proven their fundamental suitability: in future, AI could be used not only for classification but also for prognostic purposes. It is already possible to predict histological remission and outcome. However, further studies are necessary to make full use of the clinical potential of AI.

"Large language models" – AI of the future

Although it is not yet possible to make full use of current opportunities owing to a lack of regulatory provisions, progress has not come to a halt. Further models are being developed which may affect gastroenterology. "Large language models" understand and speak language. Those who pose the right question can already generate astonishing answers. These models can explain what is visible in an image. Summaries of guidelines, comparisons of versions with the differences highlighted – this is possible today. In gastroenterology, this could make documentation easier. AI is now an integral part of gastroenterology and successes are well within reach, the experts conclude.

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Scientific organization:

Prof. Cesare Hassan, Milan (Italy)
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PANCREAS

Pancreatic Tumors

Lancet Gastroenterol Hepatol. 2024;9(3):205–17

Labori KJ, Bratlie SO, Andersson B, Angelsen JH, Biörserud C, Björnsson B, Bringeland EA, Elander N, Garresori H, Grønbech JE, Haux J, Hemmingsson O, Gustafsson Liljefors M, Myklebust TÅ, Nymo LS, Peltola K, Pfeiffer P, Sallinen V, Sandström P, Sparrelid E, Stenvold H, Søreide K, Tingstedt B, Verbeke C, Öhlund D, Klint L, Dueland S, Lassen K; Nordic Pancreatic Cancer Trial-1 study group

Neoadjuvant FOLFIRINOX versus upfront surgery for resectable pancreatic head cancer (NORPACT-1): A multicenter, randomized, phase 2 trial

Background: In patients undergoing resection for pancreatic cancer, adjuvant modified fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) improves overall survival (OS) compared with alternative chemotherapy regimens. The authors aimed to compare the efficacy and safety of neoadjuvant FOLFIRINOX with the standard strategy of upfront surgery in patients with resectable pancreatic ductal adenocarcinoma (PDAC).
Methods: NORPACT-1 was a multicenter, randomized, phase 2 trial done in 12 hospitals in Denmark, Finland, Norway, and Sweden. Eligible patients were aged 18 years or older, with a WHO performance status of 0 or 1, and had a resectable tumor of the pancreatic head radiologically strongly suspected to be pancreatic adenocarcinoma. Participants were randomly assigned (3:2 before October, 2018, and 1:1 after) to the neoadjuvant FOLFIRINOX group or upfront surgery group. Patients in the neoadjuvant FOLFIRINOX group received 4 neoadjuvant cycles of FOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus then 2400 mg/m^2 over 46 hours on day 1 of each 14-day cycle), followed by surgery and adjuvant chemotherapy. Patients in the upfront surgery group underwent surgery and then received adjuvant chemotherapy. Initially, adjuvant chemotherapy was gemcitabine plus capecitabine (gemcitabine 1000 mg/m^2 over 30 minutes on days 1, 8, and 15 of each 28-day cycle and capecitabine 830 mg/m^2 twice daily for 3 weeks with 1 week of rest in each 28-day cycle; 4 cycles in the neoadjuvant FOLFIRINOX group, 6 cycles in the upfront surgery group). A protocol amendment was subsequently made to permit use of adjuvant modified FOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 150 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 2400 mg/m^2 over 46 hours on day 1 of each 14-day cycle; 8 cycles in the neoadjuvant FOLFIRINOX group, 12 cycles in the upfront surgery group). Randomization was performed with a computerized algorithm that stratified for each participating center and used a concealed block size of 2–6. Patients, investigators, and study team members were not masked to treatment allocation. The primary end point was OS at 18 months. Analyses were done in the intention-to-treat (ITT) and per-protocol (PP) populations. Safety was assessed in all patients who were randomly assigned and received at least 1 cycle of neoadjuvant or adjuvant therapy.
Findings: Between February 8, 2017, and April 21, 2021, 77 patients were randomly assigned to receive neoadjuvant FOLFIRINOX and 63 to undergo upfront surgery. All patients were included in the ITT analysis. For the PP analysis, 17 patients (22%) were excluded from the neoadjuvant FOLFIRINOX group (10 did not receive neoadjuvant therapy, 4 did not have PDAC, and 3 received another neoadjuvant regimen), and 8 (13%) were excluded from the upfront surgery group (7 did not have PDAC and 1 did not undergo surgical exploration). 61 of 77 patients (79%) in the neoadjuvant FOLFIRINOX group received neoadjuvant therapy. The proportion of patients alive at 18 months by ITT was 60% (95% confidence interval [CI]: 49–71) in the neoadjuvant FOLFIRINOX group versus 73% (95% CI: 62–84) in the upfront surgery group (p = 0.032), and median OS by ITT was 25.1 months (95% CI: 17.2–34.9) versus 38.5 months (95% CI: 27.6–not reached; hazard ratio [HR] = 1.52 [95% CI: 1.00–2.33], log-rank p = 0.050). The proportion of patients alive at 18 months in PP analysis was 57% (95% CI: 46–67) in the neoadjuvant FOLFIRINOX group versus 70% (95% CI: 55–83) in the upfront surgery group (p = 0.14), and median OS in PP population was 23.0 months (95% CI: 16.2–34.9) versus 34.4 months (95% CI: 19.4–not reached; HR = 1.46 [95% CI: 0.99–2.17], log-rank p = 0.058). In the safety population, 42 of 73 patients (58%) in the neoadjuvant FOLFIRINOX group and 19 of 47 patients (40%) in the upfront surgery group had at least 1 grade 3 or worse adverse event. 63 of 77 patients (82%) in the neoadjuvant group and 56 of 63 patients (89%) in the upfront surgery group had resection (p = 0.24). One sudden death of unknown cause and 1 COVID-19-related death occurred after the first cycle of neoadjuvant FOLFIRINOX. Adjuvant chemotherapy was initiated in 51 of 59 patients (86%) with resected PDAC in the neoadjuvant FOLFIRINOX group and 44 of 49 patients (90%) with resected PDAC in the upfront surgery group (p = 0.56). Adjuvant modified FOLFIRINOX was given to 13 patients (25%) in the neoadjuvant FOLFIRINOX group and 19 patients (43%) in the upfront surgery group. During adjuvant chemotherapy, neutropenia (11 patients [22%] in the neoadjuvant FOLFIRINOX group and 5 [11%] in the upfront surgery group) was the most common grade 3 or worse adverse event.

Interpretation: This phase 2 trial did not show a survival benefit from neoadjuvant FOLFIRINOX in resectable pancreatic ductal adenocarcinoma (PDAC) compared with upfront surgery. Implementation of neoadjuvant FOLFIRINOX was challenging. Future trials on treatment sequencing in resectable PDAC should be biomarker driven.

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Acute/Chronic Pancreatitis

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Chung MJ, Park SW, Lee KJ, Park DH, Koh DH, Lee J, Lee HS, Park JY, Bang S, Min S, Park JH, Kim SJ, Park CH

Clinical impact of pancreatic steatosis measured by CT on the risk of post-ERCP pancreatitis: A multicenter prospective trial

Background and aims: Pancreatic steatosis (PS) may be a risk factor for acute pancreatitis. Whether it is also a risk factor for post-ERCP pancreatitis (PEP) has not been evaluated. This study aimed to determine the impact of PS on PEP development.
Methods: This multicenter prospective trial enrolled 786 consecutive patients who underwent contrast-enhanced abdominal computed tomography (CT) and subsequent first-time endoscopic retrograde cholangiopancreatography (ERCP). PS was evaluated based on pancreatic attenuation on unenhanced CT images. The risk of PS for the development of PEP was evaluated using a logistic regression model.
Results: Of 527 patients included in the study, 157 (29.8%) had PS and 370 (70.2%) did not. At 24 hours after ERCP, there was a significant difference in the PEP identified in 22 patients (14.0%) in the PS group and 23 patients (6.2%) in the "no PS" (NPS) group (p = 0.017). Diabetes and hypertension were more common in the PS group than in the NPS group; no differences in dyslipidemia were found. Patients with PS had a higher risk for the development of PEP than those with NPS (odds ratio = 2.09; 95% confidence interval: 1.08–4.03). No other variables were identified as risk factors for PEP.

Conclusions: Pancreatic steatosis (PS) is a significant risk factor for post-ERCP pancreatitis for which preventive measures should be considered. Standardized measurement protocols to assess PS by computed tomography are needed.

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Ammer-Herrmenau C, Antweiler KL, Asendorf T, Beyer G, Buchholz SM, Cameron S, Capurso G, Damm M, Dang L, Frost F, Gomes A, Hamm J, Henker R, Hoffmeister A, Meinhardt C, Nawacki L, Nunes V, Panyko A, Pardo C, Phillip V, Pukitis A, Rasch S, Riekstina D, Rinja E, Ruiz-Rebollo ML, Sirtl S, Weingarten M, Sandru V, Woitalla J, Ellenrieder V, Neesse A

Gut microbiota predicts severity and reveals novel metabolic signatures in acute pancreatitis

Objective: Early disease prediction is challenging in acute pancreatitis (AP). Here, the authors prospectively investigate whether the microbiome predicts severity of AP (Pancreatitis – Microbiome As Predictor of Severity; P-MAPS) early at hospital admission.
Design: Buccal and rectal microbial swabs were collected from 424 patients with AP within 72 hours of hospital admission in 15 European centers. All samples were sequenced by full-length 16S rRNA and metagenomic sequencing using Oxford Nanopore Technologies. Primary end point was the association of the orointestinal microbiome with the revised Atlanta classification (RAC). Secondary end points were mortality, length of hospital stay and severity (organ failure > 48 hours and/or occurrence of pancreatic collections requiring intervention) as post hoc analysis. Multivariate analysis was conducted from normalized microbial and corresponding clinical data to build classifiers for predicting severity. For functional profiling, gene set enrichment analysis (GSEA) was performed and normalized enrichment scores calculated.
Results: After data processing, 411 buccal and 391 rectal samples were analyzed. The intestinal microbiome significantly differed for the RAC (Bray-Curtis, p value = 0.009), mortality (Bray-Curtis, p value = 0.006), length of hospital stay (Bray-Curtis, p value = 0.009) and severity (Bray-Curtis, p value = 0.008). A classifier for severity with 16 different species and systemic inflammatory response syndrome achieved an area under the receiving operating characteristic (AUROC) of 85%, a positive predictive value of 67% and a negative predictive value of 94% outperforming established severity scores. GSEA revealed functional pathway units suggesting elevated short-chain fatty acid production in severe AP.

Conclusions: The orointestinal microbiome predicts clinical hallmark features of acute pancreatitis, and short-chain fatty acids may be used for future diagnostic and therapeutic concepts.

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Elmunzer BJ, Foster LD, Serrano J, Coté GA, Edmundowicz SA, Wani S, Shah R, Bang JY, Varadarajulu S, Singh VK, Khashab M, Kwon RS, Scheiman JM, Willingham FF, Keilin SA, Papachristou GI, Chak A, Slivka A, Mullady D, Kushnir V, Buxbaum J, Keswani R, Gardner TB, Forbes N, Rastogi A, Ross A, Law J, Yachimski P, Chen YI, Barkun A, Smith ZL, Petersen B, Wang AY, Saltzman JR, Spitzer RL, Ordiah C, Spino C, Durkalski-Mauldin V; SVI Study Group

Indomethacin with or without prophylactic pancreatic stent placement to prevent pancreatitis after ERCP: A randomized non-inferiority trial

Background: The combination of rectally administered indomethacin and placement of a prophylactic pancreatic stent is recommended to prevent pancreatitis after endoscopic retrograde cholangiopancreatography

(ERCP) in high-risk patients. Preliminary evidence suggests that the use of indomethacin might eliminate or substantially reduce the need for stent placement, a technically complex, costly, and potentially harmful intervention.
Methods: In this randomized, non-inferiority trial conducted at 20 referral centers in the USA and Canada, patients (aged ≥ 18 years) at high risk for post-ERCP pancreatitis (PEP) were randomly assigned (1:1) to receive rectal indomethacin alone or the combination of indomethacin plus a prophylactic pancreatic stent. Patients, treating clinicians, and outcomes assessors were masked to study group assignment. The primary outcome was PEP. To declare non-inferiority, the upper bound of the 2-sided 95% confidence interval (CI) for the difference in PEP (indomethacin alone minus indomethacin plus stent) would have to be less than 5% (non-inferiority margin) in both the intention-to-treat and per-protocol populations.
Findings: Between September 17, 2015, and January 25, 2023, a total of 1950 patients were randomly assigned. PEP occurred in 145 of 975 patients (14.9%) in the indomethacin alone group and in 110 of 975 (11.3%) in the indomethacin plus stent group (risk difference 3.6%; 95% CI: 0.6–6.6; p = 0.18 for non-inferiority). A post-hoc intention-to-treat analysis of the risk difference between groups showed that indomethacin alone was inferior to the combination of indomethacin plus prophylactic stent (p = 0.011). The relative benefit of stent placement was generally consistent across study subgroups but appeared more prominent among patients at highest risk for pancreatitis. Safety outcomes (serious adverse events, intensive care unit admission, and hospital length of stay) did not differ between groups.

Interpretation: For preventing post-ERCP pancreatitis in high-risk patients, a strategy of indomethacin alone was not as effective as a strategy of indomethacin plus prophylactic pancreatic stent placement. These results support prophylactic pancreatic stent placement in addition to rectal indomethacin administration in high-risk patients, in accordance with clinical practice guidelines.

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LIVER AND BILE

HBV

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Sonneveld MJ, Chiu SM, Park JY, Brakenhoff SM, Kaewdech A, Seto WK, Tanaka Y, Carey I, Papatheodoridi M, Colombatto P, van Bömmel F, Janssen HL, Berg T, Zoulim F, Ahn SH, Dalekos GN, Erler NS, Brunetto M, Wedemeyer H, Cornberg M, Yuen MF, Agarwal K, Boonstra A, Buti M, Piratvisuth T, Papatheodoridis G, Chen CH, Maasoumy B; CREATE Study Group

HBV DNA and HBsAg levels at 24 weeks off-treatment predict clinical relapse and HBsAg loss in HBeAg-negative patients who discontinued antiviral therapy

Background and aims: Patients who discontinue nucleo(s)tide analogue therapy are at risk of viral rebound and severe hepatitis flares, necessitating intensive off-treatment follow-up.
Methods: The authors studied the association between hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA levels at off-treatment follow-up week 24 (FU W24), with subsequent clinical relapse, and HBsAg loss in a multicenter cohort of hepatitis B e antigen (HBeAg)-negative patients with chronic hepatitis B who discontinued nucleo(s)tide analogue therapy.
Results: They studied 475 patients, 82% Asian, and 55% treated with entecavir. Patients with higher HBV DNA levels at FU W24 had a higher risk of clinical relapse (hazard ratio [HR] = 1.576; p < 0.001) and a lower chance of HBsAg loss (HR = 0.454; p < 0.001). Similarly, patients with higher HBsAg levels at FU W24 had a higher risk of clinical relapse (HR = 1.579; p < 0.001) and a lower chance of HBsAg loss (HR = 0.263; p < 0.001). A combination of both HBsAg < 100 IU/ml and HBV DNA < 100 IU/ml at FU W24 identified patients with excellent outcomes (9.9% clinical relapse and 58% HBsAg loss at 216 weeks of follow-up). Conversely, relapse rates were high and HBsAg loss rates negligible among patients with both HBsAg > 100 IU/ml and HBV DNA > 100 IU/ml (p < 0.001).

Conclusions: Among hepatitis B e antigen-negative patients with chronic hepatitis B who discontinued antiviral therapy and who did not experience clinical relapse before follow-up week 24 (FU W24), serum levels of hepatitis B virus (HBV) DNA and hepatitis B surface antigen (HBsAg) at FU W24 can be used to predict subsequent clinical relapse and HBsAg clearance. A combination of HBsAg < 100 IU/ml with HBV DNA < 100 IU/ml identifies patients with a low risk of relapse and excellent chances of HBsAg loss and could potentially be used as an early surrogate end point for studies aiming at finite therapy in HBV.

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Hepatocellular carcinoma reduced, HBsAg loss increased, and survival improved after finite therapy in hepatitis B patients with cirrhosis

Background and aims: Long-term nucleos(t)ide analogue (NA) treatment can reduce hepatocellular carcinoma (HCC) in patients with hepatitis B virus-related liver cirrhosis (HBV-LC). Earlier small cohort studies showed a comparable 5-year incidence of HCC in hepatitis B e antigen (HBeAg)-negative patients with HBV-LC who stopped and those continued NA therapy. This study aimed to validate these findings using a large cohort with 10-year follow-up.
Approach and results: From 2 centers, 494 HBeAg-negative patients with HBV-LC who stopped (finite group) and 593 who continued (continuous group) NA therapy were recruited. HCC, hepatitis B surface antigen (HBsAg) loss, liver-related mortality/transplantation, and overall survival rates were compared between 2 groups with 1:1 propensity score matching of sex, treatment history, types of NA, age, transaminases, platelet count, and HBsAg levels at end of therapy in finite group or 3-year on-therapy in continuous groups. During a median follow-up of 6.2 (3.4–8.9) years, the annual and 10-year HCC incidence were lower in finite group (1.6% vs. 3.3%/year and 10-year 15.7% vs. 26.8%, respectively; log-rank test, p < 0.0001). The finite group showed greater HBsAg decline/year (-0.116 vs. -0.095 $\log_{10}$ IU/ml, p = 0.0026) and 7.6 times higher 10-year incidence of HBsAg loss (22.7% vs. 3%, p < 0.0001). Multivariate Cox regression showed finite therapy an independent factor for HBsAg loss (adjusted hazard ratio [aHR] = 11.79) but protective against HCC (aHR = 0.593), liver-related mortality/transplantation (aHR = 0.312), and overall mortality (aHR = 0.382).

Conclusions: Finite nucleos(t)ide analogue therapy in hepatitis B e antigen-negative hepatitis B virus-related liver cirrhosis may reduce incidence of hepatocellular carcinoma, increase hepatitis B surface antigen (HBsAg) loss, and improve survival. Greater HBsAg decline/loss may reflect enhanced immunity and contribute to the reduction of hepatic carcinogenesis.

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HEV

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Huang S, Zhang X, Su Y, Zhuang C, Tang Z, Huang X, Chen Q, Zhu K, Hu X, Ying D, Liu X, Jiang H, Zang X, Wang Z, Yang C, Liu D, Wang Y, Tang Q, Shen W, Cao H, Pan H, Ge S, Huang Y, Wu T, Zheng Z, Zhu F, Zhang J, Xia N

Long-term efficacy of a recombinant hepatitis E vaccine in adults: 10-year results from a randomized, double-blind, placebo-controlled, phase 3 trial

Background: Hepatitis E virus is a frequently overlooked causative agent of acute hepatitis. Evaluating the long-term durability of hepatitis E vaccine efficacy holds crucial importance.
Methods: This study was an extension to a randomized, double-blind, placebo-controlled, phase-3 clinical trial of the hepatitis E vaccine conducted in Dongtai County, Jiangsu, China. Participants were recruited from 11 townships in Dongtai County. In the initial trial, a total of 112,604 healthy adults aged 16–65 years were enrolled, stratified according to age and sex, and randomly assigned in a 1:1 ratio to receive 3 doses of hepatitis E vaccine or placebo intramuscularly at month 0, month 1, and month 6. A sensitive hepatitis E surveillance system including 205 clinical sentinels, covering the entire study region, was established and maintained for 10 years after vaccination. The primary outcome was the per-protocol efficacy of hepatitis E vaccine to prevent confirmed hepatitis E occurring at least 30 days after administration of the third dose. Throughout the study, the participants, site investigators, and laboratory staff remained blinded to the treatment assignments.
Findings: During the 10-year study period from August 22, 2007, to October 31, 2017, 90 people with hepatitis E were identified; 13 in the vaccine group (0.2 per 10,000 person-years) and 77 in the placebo group (1.4 per 10,000 person-years), corresponding to a vaccine efficacy of 83.1% (95% confidence interval [CI]: 69.4–91.4) in the modified intention-to-treat analysis and 86.6% (95% CI: 73.0–94.1) in the per-protocol analysis. In the subsets of participants assessed for immunogenicity persistence, of those who were seronegative at baseline and received 3 doses of hepatitis E vaccine, 254 of 291 vaccinees (87.3%) in Qindong at the 8.5-year mark and 1270 of 1740 vaccinees (73.0%) in Anfeng at the 7.5-year mark maintained detectable concentrations of antibodies.

Interpretation: Immunization with this hepatitis E vaccine offers durable protection against hepatitis E for up to 10 years, with vaccine-induced antibodies against hepatitis E virus persisting for at least 8.5 years.

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MASH/MASLD*

* MASH/MASLD: formerly non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD). The new international terms “MASH” (metabolic dysfunction-associated steatohepatitis) and “MASLD” (metabolic dysfunction-associated steatotic liver disease) were introduced by the multi-society Delphi panel in June 2023.

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Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, Labriola D, Moussa SE, Neff GW, Rinella ME, Anstee QM, Abdelmalek MF, Younossi Z, Baum SJ, Francque S, Charlton MR, Newsome PN, Lanthier N, Schiefke I, Mangia A, Pericàs JM, Patil R, Sanyal AJ, Noureddin M, Bansal MB, Alkhouri N, Castera L, Rudraraju M, Ratziu V; MAESTRO-NASH Investigators

A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis

Background: Non-alcoholic steatohepatitis (NASH) is a progressive liver disease with no approved treatment. Resmetirom is an oral, liver-directed, thyroid hormone receptor β-selective agonist in development for the treatment of NASH with liver fibrosis.
Methods: The authors are conducting an ongoing phase 3 trial involving adults with biopsy-confirmed NASH and a fibrosis stage of F1B, F2, or F3 (stages range from F0 [no fibrosis] to F4 [cirrhosis]). Patients were randomly assigned in a 1:1:1 ratio to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo. The 2 primary end points at week 52 were NASH resolution (including a reduction in the non-alcoholic fatty liver disease [NAFLD] activity score [NAS] by ≥ 2 points; scores range from 0–8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by at least 1 stage with no worsening of the NAS.
Results: Overall, 966 patients formed the primary analysis population (322 in the 80-mg resmetirom group, 323 in the 100-mg resmetirom group, and 321 in the placebo group). NASH resolution with no worsening of fibrosis was achieved in 25.9% of the patients in the 80-mg resmetirom group and 29.9% of those in the 100-mg resmetirom group, as compared with 9.7% of those in the placebo group ($p < 0.001$ for both comparisons with placebo). Fibrosis improvement by at least 1 stage with no worsening of the NAS was achieved in 24.2% of the patients in the 80-mg resmetirom group and 25.9% of those in the 100-mg resmetirom group, as compared with 14.2% of those in the placebo group ($p < 0.001$ for both comparisons with placebo). The change in low-density lipoprotein cholesterol levels from baseline to week 24 was -13.6% in the 80-mg resmetirom group and -16.3% in the 100-mg resmetirom group, as compared with 0.1% in the placebo group ($p < 0.001$ for both comparisons with placebo). Diarrhea and nausea were more frequent with resmetirom than with placebo. The incidence of serious adverse events was similar across trial groups: 10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg resmetirom group, and 11.5% in the placebo group.

Conclusions: Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to resolution of non-alcoholic steatohepatitis and improvement in liver fibrosis by at least 1 stage.

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Israelsen M, Torp N, Johansen S, Dalby Hansen C, Hansen ED, Thorhauge K, Kragh Hansen J, Villesen I, Bech K, Wernberg C, Andersen P, Lindvig KP, Tsochatzis EA, Thiele M, Rinella ME, Krag A; GALAXY consortium

Validation of the new nomenclature of steatotic liver disease in patients with a history of excessive alcohol intake: An analysis of data from a prospective cohort study

Background: Steatotic liver disease is a new overarching term that includes metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-related steatotic liver disease (MetALD), and alcohol-related liver disease (ALD). The authors aimed to validate the prognostic importance of MASLD, MetALD, and ALD as steatotic liver disease subclasses.
Methods: Between April 18, 2013, and September 17, 2018, they prospectively recruited patients aged 18–75 years with current or previous excessive alcohol intake (> 24 g/day for women and > 36 g/day for men) for at least a year and no previous hepatic decompensation from the Department of Gastroenterology and Hepatology at Odense University Hospital (Denmark). Participants were followed up until September 15, 2022. Here, the authors characterize these patients according to steatotic liver disease subclasses. They classified patients as having MASLD, MetALD, or ALD in accordance with the nomenclature definitions, on the basis of metabolic comorbidity and self-reported average alcohol intake in the 3 months leading up to inclusion. Histological scoring was done by a pathologist who was masked to the clinical data. Prognoses between classes were compared using Cox regression analyses on hepatic decompensation and overall mortality as the 2 outcome measures. Patients not meeting the criteria for steatotic liver disease were classified as no steatotic liver disease and served as a reference group.
Findings: 446 patients with a history of excessive alcohol intake were enrolled in this analysis (334 [75%] were male and 112 [25%] were female; median age 56 years [standard deviation 10]). Cirrhosis was present in 58 (13%), and 435 (98%) had at least 1 cardiometabolic risk factor. 321 (72%) met steatotic liver disease criteria and 125 (28%) did not have steatotic liver disease, meaning no evident liver steatosis and no significant fibrosis (≥ F2). Of the 321 patients with steatotic liver disease, 6 (2%) were identified as having ALD due to the absence of cardiometabolic risk factors. The remaining 315 patients (98%) presented with at least 1 cardiometabolic risk factor. Of these patients, 153 (49%) had MASLD, 76 (24%) had MetALD, and 86 (27%) had ALD. During follow-up, 67 of 446 patients (15%) decompensated and 97 (22%) died (median follow-up 70 months [interquartile range, 53–94]). Patients with steatotic liver disease had a significantly higher risk of hepatic decompensation and overall mortality than those without steatotic liver disease, independent of age, sex, and liver stiffness. The risk of decompensation increased in a stepwise manner from MASLD (hazard ratio [HR] = 4.73; 95% confidence interval [CI]: 1.03–21.6), through MetALD (HR = 7.69; 95% CI: 1.66–35.6), to ALD (HR = 10.2; 95% CI: 2.24–46.4). Similarly, overall mortality increased from MASLD (HR = 2.30; 95% CI: 1.08–4.90), through MetALD (HR = 2.94; 95% CI: 1.31–6.58), to ALD (HR = 3.57; 95% CI: 1.64–7.80), independent of age, sex, and liver stiffness.

Interpretation: Steatotic liver disease and its subclasses portend distinct prognoses. There is a need to specify how historical alcohol intake should be integrated into the nomenclature and risk stratification of steatotic liver disease.

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Díaz LA, Fuentes-López E, Idalsoaga F, Ayares G, Corsi O, Arnold J, Cannistra M, Vio D, Márquez-Lomas A, Ramirez-Cadiz C, Medel MP, Hernandez-Tejero M, Ferreccio C, Lazo M, Roblero JP, Cotter TG, Kulkarni AV, Kim W, Brahmania M, Louvet A, Tapper EB, Dunn W, Simonetto D, Shah VH, Kamath PS, Lazarus JV, Singal AK, Bataller R, Arrese M, Arab JP

Association between public health policies on alcohol and worldwide cancer, liver disease and cardiovascular disease outcomes

Background and aims: The long-term impact of alcohol-related public health policies (PHPs) on disease burden is unclear. The authors aimed to assess the association between alcohol-related PHPs and alcohol-related health consequences.
Methods: They conducted an ecological multinational study including 169 countries, and collected data on alcohol-related PHPs from the WHO Global Information System of Alcohol and Health 2010. Data on alcohol-related health consequences between 2010 and 2019 were obtained from the Global Burden of Disease database. PHPs were classified into 5 items, including criteria for low, moderate, and strong PHP establishment. The authors estimated an alcohol preparedness index (API) using multiple correspondence analysis (0 lowest and 100 highest establishment). They also estimated an incidence rate ratio (IRR) for outcomes according to API using adjusted multilevel generalized linear models with a Poisson family distribution.
Results: The median API in the 169 countries was 54 (interquartile range, 34.9–76.8). The API was inversely associated with alcohol use disorder (AUD) prevalence (IRR = 0.13; 95% confidence interval [CI]: 0.03–0.60; p = 0.010), alcohol-associated liver disease (ALD) mortality (IRR = 0.14; 95% CI: 0.03–0.79; p = 0.025), mortality due to neoplasms (IRR = 0.09; 95% CI: 0.02–0.40; p =

0.002), alcohol-attributable hepatocellular carcinoma (HCC) (IRR = 0.13; 95% CI: 0.02–0.65; p = 0.014), and cardiovascular diseases (IRR = 0.09; 95% CI: 0.02–0.41; p = 0.002). The highest associations were observed in the Americas, Africa, and Europe. These associations became stronger over time, and AUD prevalence was significantly lower after 2 years, while ALD mortality and alcohol-attributable HCC incidence decreased after 4 and 8 years from baseline API assessment, respectively (p < 0.05).

Conclusions: The alcohol preparedness index (API) is a valuable instrument to quantify the robustness of alcohol-related public health policy (PHP) establishment. Lower alcohol use disorder prevalence and lower mortality related to alcohol-associated liver disease, neoplasms, alcohol-attributable hepatocellular carcinoma, and cardiovascular diseases were observed in countries with a higher API. These results encourage the development and strengthening of alcohol-related policies worldwide.

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AIH/PBC/PSC

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Hirschfield GM, Bowlus CL, Mayo MJ, Kremer AE, Vierling JM, Kowdley KV, Levy C, Villamil A, Ladrón de Guevara Cetina AL, Janczewska E, Zigmond E, Jeong SH, Yilmaz Y, Kallis Y, Corpechot C, Buggisch P, Invernizzi P, Londoño Hurtado MC, Bergheanu S, Yang K, Choi YJ, Crittenden DB, McWherter CA; RESPONSE Study Group

A phase 3 trial of seladelpar in primary biliary cholangitis

Background: Effective treatments for patients with primary biliary cholangitis are limited. Seladelpar, a peroxisome proliferator-activated receptor δ agonist, has potential benefits.
Methods: In this phase 3, 12-month, double-blind, placebo-controlled trial, the authors randomly assigned (in a 2:1 ratio) patients who had had an inadequate response to or who had a history of unacceptable side effects with ursodeoxycholic acid (UDCA) to receive oral seladelpar at a dose of 10 mg daily or placebo. The primary end point was a biochemical response, which was defined as an alkaline phosphatase (ALP) level < 1.67 times the upper limit of the normal range, with a decrease of ≥ 15% from baseline, and a normal total bilirubin level at month 12. Key secondary end points were normalization of the ALP level at month 12 and a change in the score on the pruritus numerical rating scale (range, 0 [no itch] to 10 [worst itch imaginable]) from baseline to month 6 among patients with a baseline score of at least 4 (indicating moderate-to-severe pruritus).
Results: Of the 193 patients who underwent randomization and treatment, 93.8% received UDCA as standard-of-care background therapy. A greater percentage of the patients in the seladelpar group than in the placebo group had a biochemical response (61.7% vs. 20.0%; difference, 41.7 percentage points; 95% confidence interval [CI]: 27.7–53.4; p < 0.001). Normalization of the ALP level also occurred in a greater percentage of patients who received seladelpar than of those who received placebo (25.0% vs. 0%; difference, 25.0 percentage points; 95% CI: 18.3–33.2; p < 0.001). Seladelpar resulted in a greater reduction in the score on the pruritus numerical rating scale than placebo (least-squares mean change from baseline, -3.2 vs. -1.7; least-squares mean difference, -1.5; 95% CI: -2.5 to -0.5; p = 0.005). Adverse events were reported in 86.7% of the patients in the seladelpar group and in 84.6% in the placebo group, and serious adverse events in 7.0% and 6.2%, respectively.

Conclusions: In this trial involving patients with primary biliary cholangitis, the percentage of patients who had a biochemical response and alkaline phosphatase normalization was significantly greater with seladelpar than with placebo. Seladelpar also significantly reduced pruritus among patients who had moderate-to-severe pruritus at baseline. The incidence and severity of adverse events were similar in the 2 groups.

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Corpechot C, Lemoinne S, Soret PA, Hansen B, Hirschfield G, Gulamhusein A, Montano-Loza AJ, Lytvyak E, Pares A, Olivas I, Eaton JE, Osman KT, Schramm C, Sebode M, Lohse AW, Dalekos G, Gatselis N, Nevens F, Cazzagon N, Zago A, Russo FP, Floreani A, Abbas N, Trivedi P, Thorburn D, Saffioti F, Barkai L, Roccarina D, Calvaruso V, Fichera A, Delamarre A, Sobenko N, Villamil AM, Medina-Morales E, Bonder A, Patwardhan V, Rigamonti C, Carbone M, Invernizzi P, Cristoferi L, van der Meer A, de Veer R, Zigmond E, Yehezkel E, Kremer AE, Deibel A, Bruns T, Große K, Wetten A, Dyson JK, Jones D, Dumortier J, Pageaux GP, de Lédinghen V, Chazouillères O, Carrat F; Global & ERN Rare-Liver PBC Study Groups

Adequate versus deep response to ursodeoxycholic acid in primary biliary cholangitis: To what extent and under what conditions is normal alkaline phosphatase level associated with complication-free survival gain?

Background and aims: Normal alkaline phosphatase (ALP) levels in ursodeoxycholic acid (UDCA)-treated patients with primary biliary cholangitis (PBC) are associated with better long-term outcome. However, second-line therapies are currently recommended only when ALP levels remain above 1.5 times the upper limit of normal (x ULN) after 12-month UDCA. The authors assessed whether, in patients considered good responders to UDCA, normal ALP levels were associated with significant survival gains.
Approach and results: They performed a retrospective cohort study of 1047 patients with PBC who attained

an adequate response to UDCA according to Paris-2 criteria. Time to liver-related complications, liver transplantation, or death was assessed using adjusted restricted mean survival time (RMST) analysis. The overall incidence rate of events was 17.0 (95% confidence interval [CI]: 13.7–21.1) per 1000 out of 4763.2 patient-years. On the whole population, normal serum ALP values (but not normal gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), or aspartate aminotransferase (AST); or total bilirubin < 0.6 x ULN) were associated with a significant absolute complication-free survival gain at 10 years (mean 7.6 months, 95% CI: 2.7–12.6; p = 0.003). In subgroup analysis, this association was significant in patients with a liver stiffness measurement ≥ 10 kPa and/or age ≤ 62 years, with a 10-year absolute complication-free survival gain of 52.8 months (95% CI: 45.7–59.9; p < 0.001) when these 2 conditions were met.

Conclusions: Primary biliary cholangitis patients with an adequate response to ursodeoxycholic acid and persistent alkaline phosphatase elevation between 1.1 and 1.5 times the upper limit of normal, particularly those with advanced fibrosis and/or who are sufficiently young, remain at risk of poor outcome. Further therapeutic efforts should be considered for these patients.

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Åberg F, Sallinen V, Tuominen S, Adam R, Karam V, Mirza D, Heneghan MA, Line PD, Bennet W, Ericzon BG, Grat M, Lodge P, Rasmussen A, Schmelzle M, Thorburn D, Fondevila C, Helanterä I, Nordin A; European Liver and Intestine Transplant Association (ELITA)

Cyclosporine vs. tacrolimus after liver transplantation for primary sclerosing cholangitis – A propensity score-matched intention-to-treat analysis

Background and aims: There is controversy regarding the optimal calcineurin inhibitor type after liver transplant(ation) (LT) for primary sclerosing cholangitis (PSC). The authors compared tacrolimus with cyclosporine in a propensity score-matched intention-to-treat analysis based on registries representing nearly all LTs in Europe and the US.
Methods: From the European Liver Transplant Registry (ELTR) and Scientific Registry of Transplant Recipients (SRTR), they included adult patients with PSC undergoing a primary LT between 2000–2020. Patients initially treated with cyclosporine were propensity score-matched 1:3 with those initially treated with tacrolimus. The primary outcomes were patient and graft survival rates.
Results: The propensity score-matched sample comprised 399 cyclosporine-treated and 1197 tacrolimus-treated patients with PSC. During a median follow-up of 7.4 years (interquartile range, 2.3–12.8, 12,579.2 person-years), there were 480 deaths and 231 re-LTs. The initial tacrolimus treatment was superior to cyclosporine in terms of patient and graft survival, with 10-year patient survival estimates of 72.8% for tacrolimus and 65.2% for cyclosporine (p < 0.001) and 10-year graft survival estimates of 62.4% and 53.8% (p < 0.001), respectively. These findings were consistent in the subgroups according to age, sex, registry (ELTR vs. SRTR), time period of LT, Model for End-stage Liver Disease (MELD) score, and diabetes status. The acute rejection rates were similar between groups. In the multivariable Cox regression analysis, tacrolimus (hazard ratio [HR] = 0.72, p < 0.001) and mycophenolate use (HR = 0.82, p = 0.03) were associated with a reduced risk of graft loss or death, whereas steroid use was not significant.

Conclusions: Tacrolimus is associated with better patient and graft survival rates than cyclosporine and should be the standard calcineurin inhibitor used after liver transplantation for patients with primary sclerosing cholangitis.

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Slooter CD, van den Brand FF, Lleo A, Colapietro F, Lenzi M, Muratori P, Kerkar N, Dalekos GN, Zachou K, Lucena MI, Robles-Díaz M, Di Zeo-Sánchez DE, Andrade RJ, Montano-Loza AJ, Lytvyak E, Lissenberg-Witte BI, Maisonneuve P, Bouma G, Macedo G, Liberal R, de Boer YS; Dutch AIH Study Group; International Autoimmune Hepatitis Group

Lack of complete biochemical response in autoimmune hepatitis leads to adverse outcome: First report of the IAIHG retrospective registry

Background and aims: The International Autoimmune Hepatitis Group retrospective registry (IAIHG-RR) is a web-based platform with subjects enrolled with a clinical diagnosis of autoimmune hepatitis (AIH). As prognostic factor studies with enough power are scarce, this study aimed to ascertain data quality and identify prognostic factors in the IAIHG-RR cohort.
Methods: This retrospective, observational, multicenter study included all patients with a clinical diagnosis of AIH from the IAIHG-RR. The quality assessment consisted of external validation of completeness and consistency for 29 predefined variables. Cox regression was used to identify risk factors for liver-related death and liver transplantation (LT).
Results: This analysis included 2559 patients across 7 countries. In 1700 patients, follow-up was available, with a completeness of individual data of 90% (range, 30–100). During a median follow-up period of 10 (range, 0–49) years, there were 229 deaths, of which 116 were liver-related, and 143 patients underwent LT. Non-White ethnicity (hazard ratio [HR] = 4.1; 95% confidence interval [CI]: 2.3–7.1), cirrhosis (HR = 3.5; 95% CI: 2.3–5.5), variant syndrome with primary sclerosing cholangitis (PSC) (HR = 3.1; 95% CI: 1.6–6.2), and lack of complete

biochemical response within 6 months (HR = 5.7; 95% CI: 3.4–9.6) were independent prognostic factors.

Conclusions: The International Autoimmune Hepatitis Group retrospective registry (IAIHG-RR) represents the world's largest autoimmune hepatitis (AIH) cohort with moderate-to-good data quality and a relevant number of liver-related events. The registry is a suitable platform for patient selection in future studies. Lack of complete biochemical response to treatment, non-White ethnicity, cirrhosis, and PSC-AIH were associated with liver-related death and liver transplantation.

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Kowdley KV, Bowlus CL, Levy C, Akarca US, Alvares-da-Silva MR, Andreone P, Arrese M, Corpechot C, Francque SM, Heneghan MA, Invernizzi P, Jones D, Kruger FC, Lawitz E, Mayo MJ, Shiffman ML, Swain MG, Valera JM, Vargas V, Vierling JM, Villamil A, Addy C, Dietrich J, Germain JM, Mazain S, Rafailovic D, Taddé B, Miller B, Shu J, Zein CO, Schattenberg JM; ELATIVE Study Investigators' Group

Efficacy and safety of elafibranor in primary biliary cholangitis

Background: Primary biliary cholangitis (PBC) is a rare, chronic cholestatic liver disease characterized by the destruction of interlobular bile ducts, leading to cholestasis and liver fibrosis. Whether elafibranor, an oral, dual peroxisome proliferator-activated receptor α and δ agonist, may have benefit as a treatment for PBC is unknown.
Methods: In this multinational, phase 3, double-blind, placebo-controlled trial, the authors randomly assigned (in a 2:1 ratio) patients with PBC who had had an inadequate response to or unacceptable side effects with ursodeoxycholic acid to receive once-daily elafibranor, at a dose of 80 mg, or placebo. The primary end point was a biochemical response (defined as an alkaline phosphatase [ALP] level of < 1.67 times the upper limit of the normal range, with a reduction of ≥ 15% from baseline, and normal total bilirubin levels) at week 52. Key secondary end points were normalization of the ALP level at week 52 and a change in pruritus intensity from baseline through week 52 and through week 24, as measured on the Worst Itch Numeric Rating Scale (WI-NRS; scores range from 0 [no itch] to 10 [worst itch imaginable]).
Results: A total of 161 patients underwent randomization. A biochemical response (the primary end point) was observed in 51% of the patients (55/108) who received elafibranor and in 4% (2/53) who received placebo, for a difference of 47 percentage points (95% confidence interval [CI]: 32–57; p < 0.001). The ALP level normalized in 15% of the patients in the elafibranor group and in none of the patients in the placebo group at week 52 (difference, 15 percentage points; 95% CI: 6–23; p = 0.002). Among patients who had moderate-to-severe pruritus (44 patients in the elafibranor group and 22 in the placebo group), the least-squares mean change from baseline through week 52 on the WI-NRS did not differ significantly between the groups (-1.93 vs. -1.15; difference, -0.78; 95% CI: -1.99–0.42; p = 0.20). Adverse events that occurred more frequently with elafibranor than with placebo included abdominal pain, diarrhea, nausea, and vomiting.

Conclusions: Treatment with elafibranor resulted in significantly greater improvements in relevant biochemical indicators of cholestasis than placebo.

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Colapietro F, Maisonneuve P, Lytvyak E, Beuers U, Verdonk RC, van der Meer AJ, van Hoek B, Kuiken SD, Brouwer JT, Muratori P, Aghemo A, Carella F, van den Berg AP, Zachou K, Dalekos GN, Di Zeo-Sánchez DE, Robles M, Andrade RJ, Montano-Loza AJ, van den Brand FF, Slooter CD, Macedo G, Liberal R, de Boer YS, Lleo A; Dutch AIH Study Group; International Autoimmune Hepatitis Group

Incidence and predictors of hepatocellular carcinoma in patients with autoimmune hepatitis

Background and aims: Autoimmune hepatitis (AIH) is a rare chronic liver disease of unknown etiology; the risk of hepatocellular carcinoma (HCC) remains unclear and risk factors are not well-defined. The authors aimed to investigate the risk of HCC across a multicenter AIH cohort and to identify predictive factors.
Methods: They performed a retrospective, observational, multicentric study of patients included in the International Autoimmune Hepatitis Group Retrospective Registry. The assessed clinical outcomes were HCC development, liver transplantation, and death. Fine and Gray regression analysis stratified by center was applied to determine the effects of individual covariates; the cumulative incidence of HCC was estimated using the competing risk method with death as a competing risk.
Results: A total of 1428 patients diagnosed with AIH from 1980 to 2020 from 22 eligible centers across Europe and Canada were included, with a median follow-up of 11.1 years (interquartile range, 5.2–15.9). 293 patients (20.5%) had cirrhosis at diagnosis. During follow-up, 24 patients developed HCC (1.7%), an incidence rate of 1.44 cases/1000 patient-years; the cumulative incidence of HCC increased over time (0.6% at 5 years, 0.9% at 10 years, 2.7% at 20 years, and 6.6% at 30 years of follow-up). Patients who developed cirrhosis during follow-up had a significantly higher incidence of HCC. The cumulative incidence of HCC was 2.6%, 4.6%, 5.6% and 6.6% at 5, 10, 15, and 20 years after the development of cirrhosis, respectively. Obesity (hazard ratio [HR] = 2.94, p = 0.04), cirrhosis (HR = 3.17, p = 0.01), and AIH/primary sclerosing cholangitis variant syndrome (HR = 5.18, p = 0.007) at baseline were independent risk factors for HCC development.

Conclusions: Incidence of hepatocellular carcinoma in autoimmune hepatitis (AIH) is low even after cirrhosis development and is associated with risk factors including obesity, cirrhosis, and AIH-PSC variant syndrome.

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HCC

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Celsa C, Cabibbo G, Fulgenzi CAM, Scheiner B, D'Alessio A, Manfredi GF, Nishida N, Ang C, Marron TU, Saeed A, Wietharn B, Pinter M, Cheon J, Huang YH, Lee PC, Phen S, Gampa A, Pillai A, Vivaldi C, Salani F, Masi G, Roehlen N, Thimme R, Vogel A, Schönlein M, von Felden J, Schulze K, Wege H, Galle PR, Kudo M, Rimassa L, Singal AG, El Tomb P, Ulahannan S, Parisi A, Chon HJ, Hsu WF, Stefanini B, Verzoni E, Giusti R, Veccia A, Catino A, Aprile G, Guglielmini PF, Di Napoli M, Ermacora P, Antonuzzo L, Rossi E, Verderame F, Zustovich F, Ficorella C, Di Pietro FR, Battelli N, Negrini G, Grossi F, Bordonaro R, Pipitone S, Banzi M, Ricciardi S, Laera L, Russo A, De Giorgi U, Cavanna L, Sorarù M, Montesarchio V, Bordi P, Brunetti L, Pinto C, Bersanelli M, Cammà C, Cortellini A, Pinato DJ

Characteristics and outcomes of immunotherapy-related liver injury in patients with hepatocellular carcinoma versus other advanced solid tumors

Background and aims: Immune-related liver injury (irLI) is commonly observed in patients with cancer treated with immune checkpoint inhibitors (ICIs). The aim of this study was to compare the incidence, clinical characteristics, and outcomes of irLI between patients receiving ICIs for hepatocellular carcinoma (HCC) versus other solid tumors.
Methods: Two separate cohorts were included: 375 patients with advanced/unresectable HCC, Child-Pugh A class treated with first-line atezolizumab and bevacizumab from the AB-real study, and a non-HCC cohort including 459 patients treated with first-line ICI therapy from the INVIDIa-2 multicenter study. IrLI was defined as a treatment-related increase of aminotransferase levels after exclusion of alternative etiologies of liver injury. The incidence of irLI was adjusted for the duration of treatment exposure.
Results: In patients with HCC, the incidence of any grade irLI was 11.4% over a median treatment exposure of 4.4 months (95% confidence interval [CI]: 3.7–5.2) versus 2.6% in the INVIDIa-2 cohort over a median treatment exposure of 12.4 months (95% CI: 11.1–14.0). Exposure-adjusted incidence of any grade irLI was 22.1 per 100 patient-years in patients with HCC and 2.1 per 100 patient-years in patients with other solid tumors ($p < 0.001$), with median time-to-irLI of 1.4 and 4.7 months, respectively. Among patients who developed irLI, systemic corticosteroids were administered in 16.3% of patients with HCC and 75.0% of those without HCC ($p < 0.001$), and irLI resolution was observed in 72.1% and 58.3%, respectively ($p = 0.362$). In patients with HCC, rates of hepatic decompensation and treatment discontinuation due to irLI were 7%. Grade 1–2 irLI was associated with improved overall survival only in patients with HCC (hazard ratio = 0.53, 95% CI: 0.29–0.96).

Conclusions: Despite higher incidence and earlier onset, immune-related liver injury (irLI) in patients with hepatocellular carcinoma is characterized by higher rates of remission and lower requirement for corticosteroid therapy (vs. irLI in other solid tumors), low risk of hepatic decompensation and treatment discontinuation, not negatively affecting oncological outcomes.

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Daher D, Seif El Dahan K, Cano A, Gonzales M, Ransom C, Jaurez E, Carranza O, Quirk L, Morgan T, Gopal P, Patel MS, Lieber S, Louissaint J, Cotter TG, VanWagner LB, Yang JD, Parikh ND, Yopp A, Rich NE, Singal AG

Hepatocellular carcinoma surveillance patterns and outcomes in patients with cirrhosis

Background and aims: Hepatocellular carcinoma (HCC) surveillance is associated with improved early detection and reduced mortality, although practice patterns and effectiveness vary in clinical practice. The authors aimed to characterize HCC surveillance patterns in a large, diverse cohort of patients with HCC.
Methods: They conducted a retrospective cohort study of patients diagnosed with HCC between January 2008 and December 2022 at 2 large US health systems. They recorded imaging receipt in the year before HCC diagnosis: ultrasound plus α-fetoprotein (AFP), ultrasound alone, multiphasic contrast-enhanced computed tomography (CT)/magnetic resonance imaging (MRI), and no liver imaging. Multivariable logistic and Cox regression analysis were used to compare early tumor detection, curative treatment receipt, and overall survival between surveillance strategies.
Results: Among 2028 patients with HCC (46.7% Barcelona Clinic Liver Cancer stage A), 703 (34.7%) had ultrasound plus AFP, 293 (14.5%) had ultrasound alone, 326 (16.1%) had multiphasic CT/MRI, and 706 (34.8%) had no imaging in the year before HCC diagnosis. Over the study period, proportions without imaging were stable, whereas use of CT/MRI increased. Compared with no imaging, CT/MRI and ultrasound plus AFP, but not ultrasound alone, were associated with early-stage HCC detection and curative treatment. Compared with ultrasound alone, CT/MRI and ultrasound plus AFP were associated with increased early-stage detection.

Conclusions: Hepatocellular carcinoma surveillance patterns vary in clinical practice and are associated with differing clinical outcomes. While awaiting data

to determine if computed tomography or magnetic resonance imaging surveillance can be performed in a cost-effective manner in selected patients, α-feto-protein has a complementary role to ultrasound-based surveillance, supporting its adoption in practice guidelines.

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Campani C, Vallot A, Ghannouchi H, Allaire M, Evain M, Sultanik P, Sidali S, Blaise L, Thabut D, Nahon P, Seror O, Ganne-Carrié N, Nault JC, Wagner M, Sutter O

Impact of radiological response and pattern of progression in patients with HCC treated by atezolizumab-bevacizumab

Background and aims: The authors aim to assess the role of radiological response to atezolizumab-bevacizumab in patients with hepatocellular carcinoma (HCC) to predict overall survival.
Approach and results: They retrospectively included patients with HCC treated by atezolizumab-bevacizumab in 2 tertiary centers. A retrospective blinded analysis was performed by 2 radiologists to assess Response Evaluation Criteria in Solid Tumor (RECIST 1.1) and modified RECIST (mRECIST) criteria at 12 weeks. Imaging response and treatment decisions in the multidisciplinary tumor board at 12 weeks were registered. Among 125 patients, 9.6% and 20.8% had a response, 39.2% and 35.2% had stable disease, and 51.2% and 44% had progression, according to RECIST 1.1 and mRECIST, respectively, with a substantial interobserver agreement (k coefficient = 0.79). Metastasis was independently associated with a higher risk of progression. Patients classified as responders did not reach median survival, which was 16.2 and 15.9 months for patients classified as stable and 9.1 and 9.0 months for patients classified as progressors, in RECIST 1.1 and mRECIST criteria, respectively. The authors observed a wide variability in the identification of progression in the multidisciplinary tumor board in clinical practice compared with the blind evaluation by radiologists mainly due to discrepancy in the evaluation of the increase in size of intrahepatic lesions. The appearance of new extrahepatic lesions or vascular invasion lesions was associated with a worse overall survival (p = 0.032).

Conclusions: RECIST 1.1 and mRECIST criteria predict overall survival with more responders identified by mRECIST and the appearance of new extrahepatic lesion or vascular invasion was associated with a poor prognosis. A noticeable discrepancy was observed between patients classified as progressors at reviewing and the decision reached during the multidisciplinary tumor board.

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DILI

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Ma Z, Li M, Wang Y, Zou C, Wang Y, Guo T, Su Y, Zhang M, Meng Y, Jia J, Zhang J, Zou Z, Zhao X

Association of BMI with mortality in drug-induced liver injury

Background: To clarify the associations between body mass index (BMI) and the incidences of all-cause death or liver-related death (LRD)/liver transplantation (LT) in drug-induced liver injury (DILI).
Methods: DILI patients from 3 hospitals were retrospectively retrieved and follow-up from 2009 to 2021. They were categorized into underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–23.9 kg/m^2), overweight (BMI 24–27.9 kg/m^2) and obese (BMI ≥ 28 kg/m^2) groups. Cox regression models were conducted to reveal the effect of BMI on all-cause death or LRD/LT.
Results: A total of 1469 eligible DILI patients were included: underweight 73 (4.97%), normal weight 811 (55.21%), overweight 473 (32.20%) and obese 112 (7.62%). 89 patients (6.06%) had all-cause death, of which 66 patients (4.49%) had LRD/LT. The median age was 52 years, and 1039 patients (70.73%) were female. The associations between BMI and all-cause mortality (non-linear test p < 0.01) or liver-related mortality/LT (non-linear test p = 0.01) were J-shaped. Multivariate Cox regression analysis showed that underweight (hazard ratio [HR] = 3.02, 95% confidence interval [CI]: 1.51–6.02) was significantly associated with all-cause mortality after adjusting for age and sex. Furthermore, obese males were significantly associated with liver-related mortality/LT (HR = 3.49, 95% CI: 1.13–10.72) after additional adjustment for serological indices and comorbidities.

Conclusion: Association between body mass index (BMI) and mortality is a J-shape. The overall mortality was significantly higher in underweight and obese groups. Male obesity is independently associated with liver-related death/liver transplantation. These findings indicate that patients with drug-induced liver injury with extreme BMI would have a high risk of dismal outcomes, which warrants extra medical care.

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Liver Cirrhosis

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Gratacós-Ginès J, Bruguera P, Pérez-Guasch M, López-Lazcano A, Borràs R, Hernández-Évole H, Pons-Cabrera MT, Lligoña A, Bataller R, Ginès P, López-Pelayo H, Pose E

Medications for alcohol use disorder promote abstinence in alcohol-associated cirrhosis: Results from a systematic review and meta-analysis

Background and aims: The role of medications for alcohol use disorder (MAUD) in patients with cirrhosis is not well established. Evidence on the efficacy and safety of these drugs in these patients is scarce.
Approach and results: The authors performed a systematic review and meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol guidelines on the efficacy of MAUD in patients with cirrhosis. A search was conducted in PubMed, Embase, and Scopus, including all studies until May 2022. The population was defined as patients with AUD and cirrhosis. The primary outcome was alcohol abstinence. Safety was a secondary outcome. A random-effect analysis was performed and the results were expressed as relative risk of alcohol consumption. Heterogeneity was measured by I^2. Out of 4095 unique references, 8 studies on 4 different AUD treatments (baclofen [n = 6], metadoxine [n = 1], acamprosate [n = 1], and fecal microbiota transplant [n = 1]) in a total of 794 patients were included. Four were cohort studies, and 4 were randomized controlled trials (RCTs). Only RCTs were included in the meta-analysis. MAUD was associated with a reduced rate of alcohol consumption (relative risk = 0.68; 95% confidence interval: 0.48–0.97; p = 0.03), increasing alcohol abstinence by 32% compared to placebo or standard treatment, despite high heterogeneity (I^2 = 67%). Regarding safety, out of 165 serious adverse events in patients treated with MAUD, only 5 (3%) were possibly or probably related to study medications.

Conclusion: Medications for alcohol use disorder (MAUD) in patients with cirrhosis are effective in promoting alcohol abstinence and have a good safety profile. Larger studies on the effects of MAUD are needed, especially in patients with advanced liver disease.

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Elhence H, Dodge JL, Lee BP

Association of renin-angiotensin system inhibition with liver-related events and mortality in compensated cirrhosis

Background and aims: While renin-angiotensin system inhibition lowers the hepatic venous gradient, the effect on more clinically meaningful end points is less studied. The authors aimed to quantify the relationship between renin-angiotensin system inhibition and liver-related events (LREs) among adults with compensated cirrhosis.
Methods: In this national cohort study using the Optum database, they quantified the association between angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) use and LREs (hepatocellular carcinoma, liver transplantation, ascites, hepatic encephalopathy, or variceal bleeding) among patients with cirrhosis between 2009 and 2019. Selective beta-blocker (SBB) users served as the comparator group. Demographic and clinical features were used to calculate inverse-probability treatment weighting-weighted cumulative incidences, absolute risk differences, and Cox proportional hazard ratios.
Results: Among 4214 adults with cirrhosis, 3155 were ACE inhibitor/ARB users and 1059 were SBB users. In inverse probability treatment weighting-weighted analyses, ACE inhibitor/ARB (vs. SBB) users had lower 5-year cumulative incidence (30.6% [95% confidence interval {CI}: 27.8–33.2%] vs. 41.3% [95% CI: 34.0–47.7%]; absolute risk difference, -10.7% [95% CI: -18.1% to -3.6%]) and lower risk of LREs (adjusted hazard ratio [aHR] = 0.69; 95% CI: 0.60–0.80). There was a dose-response relationship: compared with SBB use, ACE inhibitor/ARB prescriptions ≥ 1 defined daily dose (aHR = 0.65; 95% CI: 0.56–0.76) were associated with a greater risk reduction compared with < 1 defined daily dose (aHR = 0.87; 95% CI: 0.71–1.07). Results were robust across sensitivity analyses such as comparing ACE inhibitor/ARB users with non-users and as-treated analysis.

Conclusions: In this national cohort study, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use was associated with significantly lower risk of liver-related events in patients with compensated cirrhosis. These results provide support for a randomized clinical trial to confirm clinical benefit.

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Lv Y, Bai W, Zhu X, Xue H, Zhao J, Zhuge Y, Sun J, Zhang C, Ding P, Jiang Z, Zhu X, Ren W, Li Y, Zhang K, Zhang W, Li K, Wang Z, Luo B, Li X, Yang Z, Guo W, Xia D, Xie H, Pan Y, Yin Z, Fan D, Han G

Development and validation of a prognostic score to identify the optimal candidate for pre-emptive TIPS in patients with cirrhosis and acute variceal bleeding

Background and aim: Baveno VII workshop recommends the use of pre-emptive transjugular intrahepatic portosystemic shunt (p-TIPS) in patients with cirrhosis and acute variceal bleeding (AVB) at high risk of treatment failure. However, the criteria defining "high risk" have low clinical accessibility or include subjective variables. The authors aimed to develop and externally validate a model for better identification of p-TIPS candidates.

Approach and results: The derivation cohort included 1554 patients with cirrhosis and AVB who were treated with endoscopy plus drug (n = 1264) or p-TIPS (n = 290) from 12 hospitals in China between 2010 and 2017. The authors first used competing risk regression to develop a score for predicting 6-week and 1-year mortality in patients treated with endoscopy plus drugs, which included age, albumin, bilirubin, international normalized ratio, white blood cell, creatinine, and sodium. The score was internally validated with the bootstrap method, which showed good discrimination (6-week/1-year concordance-index: 0.766/0.740) and calibration, and outperformed other currently available models. In the second stage, the developed score was combined with treatment and their interaction term to predicate the treatment effect of p-TIPS (mortality risk difference between treatment groups) in the whole derivation cohort. The estimated treatment effect of p-TIPS varied substantially among patients. The prediction model had good discriminative ability (6-week/1-year c-for-benefit: 0.696/0.665) and was well calibrated. These results were confirmed in the validation dataset of 445 patients with cirrhosis with AVB from 6 hospitals in China between 2017 and 2019 (6-week/1-year c-for-benefit: 0.675/0.672).

Conclusions: The authors developed and validated a clinical prediction model that can help to identify individuals who will benefit from pre-emptive transjugular intrahepatic portosystemic shunt, which may guide clinical decision-making.

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Murray SM, Pose E, Wittner M, Londoño MC, Schaub G, Cook J, Dimitriadis S, Meacham G, Irwin S, Lim Z, Duengelhoef P, Sterneck M, Lohse AW, Perez V, Trivedi P, Bhandal K, Mullish BH, Manousou P, Provine NM, Avitabile E, Carroll M, Tipton T, Healy S, Burra P, Klenerman P, Dunachie S, Kronsteiner B, Maciola AK, Pasqual G, Hernandez-Gea V, Garcia-Pagan JC, Lampertico P, Iavarone M, Gines P, Lütgehetmann M, Schulze zur Wiesch J, Russo FP, Barnes E, Marjot T; OCTAVE Collaborative Group; PITCH study; EASL supported COVID-Hep vaccine network

Immune responses and clinical outcomes after COVID-19 vaccination in patients with liver disease and liver transplant recipients

Background and aims: Comparative assessments of immunogenicity following different COVID-19 vaccines in patients with distinct liver diseases are lacking. SARS-CoV-2-specific T-cell and antibody responses were evaluated longitudinally after 1–3 vaccine doses, with long-term follow-up for COVID-19-related clinical outcomes.
Methods: A total of 849 participants (355 with cirrhosis, 74 with autoimmune hepatitis [AIH], 36 with vascular liver disease [VLD], 257 liver transplant recipients [LTRs] and 127 healthy controls [HCs]) were recruited from 4 countries. Standardized immune assays were performed pre and post 3 vaccine doses (V1–3).
Results: In the total cohort, there were incremental increases in antibody titers after each vaccine dose ($p < 0.0001$). Factors associated with reduced antibody responses were age and LT, whereas heterologous vaccination, prior COVID-19 and mRNA platforms were associated with greater responses. Although antibody titers decreased between post-V2 and pre-V3 ($p = 0.012$), patients with AIH, VLD, and cirrhosis had equivalent antibody responses to HCs post-V3. LTRs had lower and more heterogenous antibody titers than other groups, including post-V3 where 9% had no detectable antibodies; this was heavily influenced by intensity of immunosuppression. Vaccination increased T-cell interferon γ responses in all groups except LTRs. Patients with liver disease had lower functional antibody responses against 9 Omicron subvariants and reduced T-cell responses to Omicron BA.1-specific peptides compared to wild-type. 122 cases of breakthrough COVID-19 were reported of which 5 of 122 (4%) were severe. Of the severe cases, 4 of 5 (80%) occurred in LTRs and 2 of 5 (40%) had no serological response post-V2.

Conclusion: After 3 COVID-19 vaccines, patients with liver disease generally develop robust antibody and T-cell responses to vaccination and have mild COVID-19. However, liver transplant recipients have sustained no/low antibody titers and appear most vulnerable to severe disease.

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Nicoară-Farcău O, Han G, Rudler M, Angrisani D, Monescillo A, Torres F, Casanovas G, Bosch J, Lv Y, Dunne PDJ, Hayes PC, Thabut D, Fan D, Hernández-Gea V, García-Pagán JC; pre-emptive TIPS individual data meta-analysis; International Variceal Bleeding Study and Baveno Cooperation Study groups

Pre-emptive TIPS in high-risk acute variceal bleeding. An updated and revised individual patient data meta-analysis

Background and aims: A previous individual patient data meta-analysis (IPD-MA) showed that compared with drugs and endoscopy, the placement of transjugular portosystemic shunt within 72 hours of admission (pre-emptive transjugular intrahepatic portosystemic shunt, p-TIPS) increases the survival of high-risk patients (Child-Pugh B and active bleeding and Child-Pugh C < 14 points) with cirrhosis and acute variceal bleeding. However, the previous IPD-MA was not a 2-stage meta-analysis, did not consider the potential risk of selection

bias of observational studies, and did not include the most recent randomized clinical trial. The authors performed an updated and revised IPD-MA to reassess the efficacy of p-TIPS, addressing all previous issues.
Approach and results: They included all studies from the previous IPD-MA and searched for other possible eligible publications until September 2022. They performed a 2-stage IPD-MA of data from 8 studies (4 randomized clinical trials and 4 observational). In addition, they performed a sensitivity analysis excluding those patients dying up to the first 72 hours after admission in the Drugs+Endoscopy arms of the 4 observational studies. The primary end point was the effects of p-TIPS versus Drugs+Endoscopy on 1-year survival. The authors identified 1389 patients (342 p-TIPS and 1047 Drugs+Endoscopy). The 2-stage IPD-MA showed that p-TIPS significantly reduced the mortality in the overall population (hazard ratio = 0.43, 95% confidence interval: 0.32–0.60, p < 0.001. This effect was observed in both subgroups of patients with Child-Pugh. The sensitivity analysis confirmed the survival benefit of p-TIPS.

Conclusions: The updated 2-stage individual patient data meta-analysis confirms the significant survival advantage of pre-emptive transjugular intrahepatic portosystemic shunt (p-TIPS) in high-risk patients with cirrhosis and acute variceal bleeding. As a result, p-TIPS is recommended as the preferred first-choice treatment for these patients.

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Bile Ducts

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Hajibandeh S, Ashar S, Parry C, Ellis-Owen R, Kumar N

The risk and predictors of gallbladder cancer in patients with gallbladder polyps: A retrospective cohort study with an insight into confounding by indication

Background and aim: The authors aimed to determine the risk and predictors of gallbladder cancer in all individuals with gallbladder polyps including those who did not have cholecystectomy.
Methods: The Strengthening The Reporting Of Cohort Studies in Surgery (STROCSS) guideline was followed to conduct a retrospective cohort study. All individuals with gallbladder polyps between 2010 and 2019 were followed up to determine the risk and predictors of gallbladder cancer. The primary outcomes were gallbladder cancer and gallbladder dysplasia, and the secondary outcomes included polyp growth rate and polyp disappearance rate. Binary logistic regression analysis and receiver-operating characteristic curve analysis were conducted to evaluate the outcomes.
Results: Analysis of 438 patients showed risk of gallbladder cancer was 0.7% in all polyps (0% in polyps < 10 mm; 5.9% in polyps ≥ 10 mm). The risk of gallbladder dysplasia or cancer was 1.1% in all polyps (0% in polyps < 10 mm; 10% in polyps ≥ 10 mm). The polyp size (p = 0.0001) was predictor of cancer; however, patient's age (p = 0.1085), number of polyps (p = 0.9983), symptomatic polyps (p = 0.3267), and change in size (p = 0.9012) were not. Size of 21 mm was cut-off for risk of cancer (area under the curve [AUC]: 0.995, p < 0.001) and 11.8 mm for risk of dysplasia or cancer (AUC: 0.986, p < 0.001). The mean polyp growth rate was 0.3 mm/year and polyp disappearance rate was 16%.

Conclusions: The gallbladder polyp size remains the only predictor of malignant changes regardless of patient's age, patient's symptoms and number of polyps. The polyp growth rate is unremarkable, and a significant proportion disappears during follow-up. The authors changed their follow-up protocol with reduced number of scans and early discharge policy.

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Congresses 2024

July 3–6, 2024, Barcelona, Spain
26th Annual World Congress on Gastrointestinal Cancer
E-Mail: esmo@esmo.org
https://www.worldgicancer.com

July 4–5, 2024, Cairo, Egypt
7th Annual Conference of EARTH
Gut Health across Borders
https://earth-eg.org/

July 4–6, 2024, Seoul, South Korea
ENDO 2024 – 4th World Congress of GI Endoscopy
E-Mail: anastasiia.l@worldendo.org
https://worldendo2024.org/

July 5–6, 2024, Edinburgh, Scotland
Symposium 237
XXVII International Bile Acid Meeting: Bile Acids in Health and Disease 2024
E-Mail: meeting@falkfoundation.org
https://falkfoundation.org

July 8–12, 2024, Snowmass Village, CO, USA
46th Annual Aspen Conference on Pediatric Gastrointestinal Disease
Specialties - Gastroenterology, General Pediatrics, Transplant Hepatology
E-Mail: cme@cchmc.org
https://cchmc.cloud-cme.com

September 5–6, 2024, Paris, France
10th Paris MASH Meeting
E-Mail: contact@paris-mash.org
https://www.paris-mash.org

September 9–11, 2024, Santiago, Chile
XXIX Congress of the Latin American Association for the Study of the Liver (ALEH 2024)
E-Mail: info@alehlatam.org
https://congresoaleh.com/

September 12–13, 2024, Interlaken, Switzerland
Jahreskongress 2024
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der Schweizerischen Gesellschaft für Viszeralchirurgie / SGVC
der Swiss Association for the Study of the Liver / SASL
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https://www.sggssg.ch/veranstaltungen-sgg/jahreskongress
https://sgg-sgvc-sasl.unibas.ch/

September 12–14, 2024, Porto, Portugal
37th Workshop of the European Helicobacter and Microbiota Study Group – EHMSG 2024
E-Mail: workshop@ehmsg.org
https://www.ehmsg.org/
https://www.workshop.ehmsg.org

September 14–16, 2024, Adelaide, Australia
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E-Mail: gesa@gesa.org.au
https://www.gesa.org.au/

September 18–20, 2024, Salzburg, Austria
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https://www.oegim.at

September 19–21, 2024, Marseille, France
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https://eus-endo.org/

September 19–21, 2024, Denver, CO, USA
Mayo Clinic Innovations in Gastroenterology and Hepatology 2024: AI and Beyond
E-Mail: cme@mayo.edu
https://ce.mayo.edu/

September 22–24, 2024, Edinburgh, Scotland
20th ISDE World Congress of Esophageal Diseases
E-Mail: isde-congress@isde.net
https://isde-congress.net/

September 25–27, 2024, Thessaloniki, Greece
19th Scientific and Annual Meeting of the European Society of Coloproctology (ESCP)
https://www.escp.eu.com

September 28–29, 2024, Mumbai, India
LiverEdge – Best of INASL-EASL
https://inasl-easl.com/

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